SECTION 1

INTRODUCTION TO WOMEN'S HEALTH INITIATIVE: CLINICAL TRIALS AND OBSERVATIONAL STUDY

INTRODUCTION

The health of women has extraordinary medical, social, and economic implications, as well as being of personal interest to women making choices about healthy behaviors. Too little research has focused on health issues unique to, or more common for, women, particularly chronic diseases in mature women. These conditions—cardiovascular disease, cancer, and osteoporosis—are the leading causes of mortality, morbidity, and declining quality of life. Thus, in 1991 the Director of the National Institutes of Health (NIH) announced the development of a research program to address these issues. This program, entitled the Women's Health Initiative (WHI), is composed of three studies: a Clinical Trial (CT), an Observational Study (OS), and a community-based study. For efficiency, the CT and OS have been combined into one program. This manual, *Vol. 2 - Procedures* describes Clinical Center (CC) operations and procedures for the CT and OS components.

1.1. Overview

One of the Women's Health Initiative's goals is to evaluate preventive approaches to cancer, cardiovascular disease, and osteoporotic fractures. The three approaches used in WHI are a low-fat eating pattern, hormone replacement therapy, and calcium and vitamin D supplementation. These interventions will be tested in a large clinical trial of postmenopausal women. The recruitment and screening of large numbers of women for the CT also affords a unique opportunity for observational studies of disease predictors (the OS).

The CT and OS will direct particular attention to the recruitment and study of minorities and medically-underserved segments of the population in a culturally sensitive manner. The information derived from these studies will be relevant to all women regardless of race, culture, or economic status.

The CT and OS are integrated into a single program to improve scientific and fiscal efficiency.

1.1.1. Clinical Trial

The CT is designed to address the major causes of mortality and morbidity in postmenopausal women, namely coronary heart disease, breast and colorectal cancer, and osteoporotic fractures. Cardiovascular disease is the most common cause of mortality in older women, accounting for 29 to 48 percent of all deaths in the age range of 50 to 79. Both absolute rates and proportional mortalities from these causes increase steeply with age. Among the cancers, breast cancer is the second most common cause of death. Even though breast cancer rates increase with age, the proportional mortality from this disease is slightly higher at younger ages. Colorectal cancer is the third most common cause of death among the cancers and the second most common incident cancer. Incidence and mortality rates of colorectal cancer increase with age. Fractures account for considerable morbidity, fragility, and loss of independence. Annual fracture incidence rates also increase with age.

The goal of the CT is to test whether or not treatments reduce the incidence of disease and subsequent morbidity and mortality. The CT is a controlled clinical trial of preventive treatments in women ages 50 to 79 years. There are three main components: hormonal replacement therapy (HRT), dietary modification (DM), and calcium/vitamin D (CaD) supplementation. The primary goal of the HRT component is to determine whether estrogen or estrogen plus progestin reduces the rate of coronary heart disease in comparison to placebo. The primary goal of DM is to determine whether or not following a low-fat eating pattern is associated with a lower rate of breast cancer and colorectal cancer. The primary goal of CaD is to learn whether or not calcium and vitamin D supplements reduce the rate of hip fracture as compared to placebo. The sample sizes chosen are large enough to test each treatment with confidence. The treatments will be tested in a partial 3 x 2 x 2 factorial design to reduce the total number of participants required. Women may participant in one, two or all three components of the CT depending upon their interest in and eligibility for each individual component.

1.1.2. Observational Study

There is a general recognition that few older women have been studied longitudinally and that major questions about prediction of chronic disease in postmenopausal women remain. This initiative, with its CT and OS, presents an opportunity to accumulate a large cohort of women, to follow them, and to determine the predictors and biological markers of disease. Integration of the findings of the OS and CT components is an efficient and effective way to achieve the following objectives:

- Screen women for participation in the CT.
- Develop risk-factor analyses for cardiovascular disease, cancer, and osteoporosis.
- Conduct surveillance of deaths and incidence of cardiovascular disease (especially coronary heart disease and stroke), cancer, and fractures. Assess psychosocial, including quality of life, changes over time.
- Use the case-control approach to study the link between subclinical markers and clinical disease.

1.2. Time Table for the Clinical Trial and Observational Study

Phase 1 - Vanguard Clinical Centers (16)		
Phase 1A - Protocol Development	09/30/92 - 05/31/93	(8 months)
Phase 1B - Training	06/01/93 - 08/31/93	(3 months)
Phase 1C - Vanguard Recruitment and Follow-Up	09/01/93 - 01/31/95	(17 months)
Phase 2 - Additional Clinical Centers (24)		
Phase 2A - Training	09/30/94 - 01/31/95	(4 months)
Phase 2B - Recruitment	02/01/95 - 08/31/96	(19 months - VCCs)
	02/01/95 - 01/31/98	(3 years - Other CCs)
Phase 2C, 2D - Follow-Up and Closeout Visits	09/01/96 - 03/30/05	(8 years, 7 months - VCCs)
	02/01/98 - 03/30/05	(7 years, 2 months - Other)
Phase 2E - Closeout Data	04/01/05 - 09/14/05	(5.5 months)
Phase 2F - Data Analysis	09/15/05 - 09/29/07	(2 years, 0.5 months)

1.3. WHI Manuals

The design and implementation of the WHI, as captured in the study Protocol, policies, procedures, interventions, and data collection instruments are described in the WHI Manuals. The primary function of these manuals is to provide common training and reference materials across all participating WHI organizations as a way of assuring the quality of the study. Each operational unit is responsible for developing its own manual describing the policies and procedures specific to that unit.

The WHI Manuals are contained in several volumes. The allocation of topics to volumes was based on the WHI staff members who would most use the various sections.

Volume 1 - Study Protocol and Policies: This manual contains the Protocol for the CT and OS, the committee structure and the policies governing the scientific conduct of the study. As this is a document written for and by WHI Investigators, procedural aspects of the study that are performed by Investigators (e.g., outcomes classification) are included in this manual.

Volume 2 - Procedures: This manual describes all CC procedures and guidelines for operations other than Nutrition Intervention. As the primary CC training and reference source, this manual serves as the standard by which CC operations are assessed. Procedures that are designated as Required in the section heading must be followed to adhere to the protocol, for consistency, and for participant safety.

Volume 3 - Forms: All standardized study forms are displayed in the Forms Manual in numerical order. Accompanying each form is a detailed set of instructions describing who completes the form, when and how each data item should be coded, and what should happen to the form when completed.

Volume 4 - Dietary Modification Intervention: The Dietary Modification (DM) Intervention Manual consists of two parts: the Group Nutritionist Manual and the Participant Manual. The Group Nutritionist Manual describes the procedures for carrying out the intervention sessions for the DM component. The Participant Manual contains information pertinent to each intervention session.

Volume 5 - Data System: This is a user's manual for the WHI computing system. Information is provided on the general hardware and software used as well as the specific WHI database, WHILMA.

Volume 6 - DXA Quality Assurance Manual for Hologic QDR-2000 Bone Densitometer: This is a user's manual for the WHI Bone Density Clinical Centers. This manual is intended as a supplement to the Hologic User's Manual.

Volume 7 - Quality Assurance: This manual provides procedures and checklists for Clinical Center QA Activities.

1.4. Study Communication

1.4.1. Lines of Communication

The success of any multi-center study depends heavily on the quality of communications. As the number of participating individuals and institutions increase, so does the need for formal channels and efficient, reliable means of communication. This version of the WHI Manual describes the current organization and procedure. Spring of 1995 will be the advent of new organizational structure and modified procedures. The current status is described here to avoid confusion. The study organization and committee structure provides the foundation for communications. Protocol, policy, or procedural issues or problems identified by any study personnel can be brought to the attention of an appropriate committee member or a designated Clinical Coordinating Center (CCC) representative. Staff groups have been identified for the clinic managers, clinic practitioners, data coordinators, lead nutritionists and recruitment coordinators. Regular conference calls for these staff groups, as well as the principal investigators, provide an opportunity for all staff to bring concerns and problems up for discussion, resolution and dissemination. These issues are initially brought to the Management or Executive Committee for consideration and/or may be referred to one of the Subcommittees of the Executive Committee for further development and consideration. Issues not clearly falling on a particular subcommittee will be assigned by the Management Committee. It is the responsibility of the subcommittees to evaluate any concerns and make recommendations to the Executive Committee for final approval.

As a body governed by committees, the minutes of each committee meeting or conference call will serve to document the course of the study. Minutes from all committee meetings or conference calls should be submitted to the CCC within one week of the meeting. All such minutes will be made available upon demand, eventually through a computer bulletin board. However, to limit the flood of paper, routine distribution will be limited. Minutes from the Management Committee will be regularly provided to the Executive Committee. Minutes from all Executive Committee meetings and calls will be routinely circulated to the PI from each institution and one designated clinic manager. Minutes from the Investigator's Committee meetings will also be provided to all PIs and clinic managers.

From time to time, the CCC will issue bulletins describing changes to study policies, procedures, or forms. These bulletins are intended to modify the existing WHI Manuals until an updated version of the manual is printed. These bulletins should be reviewed with all appropriate staff and added to the appropriate appendix of each manual when received.

Routine questions of study operations should be directed to the CCC (including the Regional Resource Center [RRC] which functions as a part of the CCC). Contact staff for each function will be identified on an ongoing basis. Please note the hours and days of coverage, including CCC institutional holidays.

CCC (FHCRC) Holidays:

January	1	New Year's Day
		Martin Luther King Day (Monday)
February		President's Day (Monday)
May		Memorial Day (Monday)
July	4	Independence Day
September		Labor Day (Monday)
November	11	Veteran's Day
		Thanksgiving (Thursday)
		Day After Thanksgiving (Friday)
December	24	Christmas Eve (or December 26)
	25	Christmas Day

1.4.2. Methods of Communication

The WHI will take full advantage of available means of communications: meetings, conference calls, personal calls, facsimile transmission (fax), regular and express mail, and electronic mail (eMAIL). The availability of

a standardized computing environment and eMAIL makes eMAIL the first choice for all but the most urgent communications. The advantages of eMAIL are speed, accuracy, reliability of communications, simplification of documentation, and cost, given the existence of the WHI network.

Electronic Mail

All WHI personnel with access to the WHI network will be given a unique user identifier. This ID and a user-defined password will be required for accessing the network and participating in the electronic messaging system. Each user will be able to send and receive messages throughout the network, store, and retrieve them electronically, and access messages for general dissemination (e.g., minutes from meetings). Groups of WHI personnel, as defined by interests or responsibilities (e.g., nutrition interventionists, lead data coordinators, subcommittees or the Executive Committee) will be established as an entity within the eMAIL system to facilitate quick and comprehensive addressing and distribution.

Access to WHI eMAIL is desirable for all affiliated institutions and individuals. Budget limitations may limit the ability of the system to reach all WHI staff. Groups not explicitly funded for access, such as various CCC subcontractors and other NIH collaborating offices will be added if funding is identified. Priorities will be based on data flow and communication needs. EMAIL connections, such as Internet, have been made available on a broad basis especially for communications with these groups. The Internet address of all WHI users is based on the CCC maintained gateway and is of the form: user name %or@hub.fhcrc.org.

Inquiry Reporting System

The eMAIL system will be used for routine inquiries between the CCs and the CCC. A paper version, *Form 171 - Inquiry Form*, may also be used if necessary.

The Inquiry Form provides a standard format for the CCs to ask questions of the CCC. The Inquiry Form allows the CC to describe problems and ask questions about any aspect of study procedures, policies, and forms.

CCs should take the following steps before completing a CC Inquiry Form:

1. Consult *Vol. 1 - Protocol*
2. Consult *Vol. 2 - Procedures* or other volumes of the WHI manuals.
3. Ask the Clinic Manager or other supervisor.
4. Ask the Principal Investigator or other Investigator.

If the question cannot be answered, the CC should complete an Inquiry and send it to the CCC. If the question is urgent (for example, involving a safety issue or randomization, being unable to dispense medication or other critical matters), the CC should call the CCC for a quicker response.

The CCC records an answer on the form and returns the Inquiry to the CC. Questions and answers recorded on the Inquiry Form are used to update the WHI Manuals or other relevant study manuals.

If an Inquiry from one CC results in a change or clarification of a procedure applicable to other CCs, the CCC issues a bulletin to all CCs. In addition, a copy of each answered Inquiry that pertains to all CCs is forwarded to each CC.

Issue Action Log

As a subset of the Inquiry Reporting System, some issues raised may require a change in protocol, study policy or procedure. Such issues may be referred to a subcommittee of the Executive Committee or Management Committee for further development and approval. Tracking of these activities, as well as the review and

approval steps within the study organization, the Data Safety and Monitoring Board, and the Director of NIH, is done with the *Issue-Action Log*.

Telephone Calls

Telephone calls are necessary to maintain rapport between individuals and to provide a forum for a "real-time" discussion. The number of participating CCs makes the number of calls received at the CCC or the Program Office potentially overwhelming unless there is discretion in their use. It is recommended that CCs establish logs of long-distance calls to the CCC and NIH to monitor their own activity.

Mail

Regular and express mail will be used to ship supplies and larger documents. Note that express mail addresses for some institutions, including the Program Office and the CCC, are different from the regular US Mail address. It is recommended that you do not send items to the Program Office by regular mail because of delays in the internal mail system at NIH.

WHI Directory

A directory of all WHI investigators and staff addresses, telephone and fax numbers are provided through the CCC. The directory is updated and distributed to all WHI personnel on a regular basis.

1.5. Contact with Primary Care Physicians

The intent of WHI is to avoid interfering with the participant's relationship with her usual source of medical care. The WHI CCs will not provide regular medical care for participants. Each CC will have a referral system for women who do not have their own physician.

Community Relations

It will be advantageous to each CC to have familiarized local physicians and medical associations about the WHI CC activities. Articles in local professional publications, presentations at local meetings, and a mailing of informational materials to the women's primary care physicians should be considered. A standard set of slides describing WHI will be provided to each CC. These may be useful for presentations to local professional or lay groups.

Providing Information to Help Them Advise Their Patients About Participation

Sometimes a potential participant will want to talk with her primary physician regarding the study and whether or not she should participate. This will occur, for example, if a woman is currently using hormone replacement therapy at the first contact. Provide her with information to take to her primary physician and ask her to visit her primary physician and discuss whether or not she can discontinue her present hormone regime. Her primary physician may also call the CC for information about the study. Each CC should decide upon a contact person(s) who will talk with these physicians. The contact person(s) should be very knowledgeable about the study and able to answer the physician's questions in detail.

Obtaining/Confirming Medical History

To avoid unnecessary duplication of services, some information about a participant's medical history (e.g., results of last mammogram) and some diagnostic study results may need to be requested from her physician. Such requests for information should be accompanied by a medical release form signed by the participant (see *Section 4.2.4.3. - Initial [Screening] Informed Consent*).

Reporting/Advising on CC-Detected Medical Conditions (Alerts)

To prevent duplication of service and subsequent charges and inconvenience or increased risk to a CT participant from repeating a procedure, results of the following procedures will be forwarded to the participant's primary physician:

- Mammography
- Pelvic Exam
- Pap Smear
- Endometrial Aspiration
- Transvaginal Endometrial Ultrasound

Community physicians and WHI participants should be informed that the CCs will <u>not</u> be measuring cholesterol or performing any blood tests that would replace the woman's routine medical care. Inform both the participant and her personal health care provider that the WHI CC is not measuring or monitoring cholesterol levels or other biochemical markers, unless the CC has made arrangements for this on an ongoing basis.

Results of other WHI measures and studies (such as CBC, ECG, bone density) will be provided to the participant or her primary physician if they indicate possible underlying serious problems. See *Section 4.3.4.4. - Procedures* for WHI alert values for procedures and measurements.

Some CCs may want to refer other measurements and procedure results to the participant's primary physician. Follow your CC's guidelines regarding additional alerts and referrals to primary physicians.

Coordinating Adverse Effect Monitoring and Management

The need to coordinate the monitoring and management of adverse effects (e.g., vaginal bleeding) may require coordination with a participant's physician(s) particularly if the physician has reported these effects to the CC. Participants in the HRT component of the CT will require such coordination more often than other CT participants (see *Section 5.4. - Managing Symptoms* and *Section 5.5. - Major Health Problems*). All physicians' requests for information should be handled in a professional manner.

Obtaining Outcome Information

Some information about outcomes may be ascertained through the participant's physician(s). Contacts to obtain this information should be courteous, professional, and as brief as possible.

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Introduction to WHI

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SECTION 2

CLINICAL CENTER GUIDELINES

INTRODUCTION

The Women's Health Initiative (WHI) Clinical Centers (CCs) have been selected, in part, because of their experience in clinical research. These guidelines are offered to help investigators at both the Vanguard Clinical Centers (VCCs) and the New Clinical Centers (NCCs) to set up satellite or remote sites and maintain their CC operations. This section can be used as a checklist to ensure that at least the essential elements are in place. It may also be helpful for staff training.

2.1 Clinical Center Facilities

Adequate and appropriate facilities are important in the overall operation of the CC. Adequate facilities are also important in maintaining participant adherence.

2.1.1 Clinic Area

2.1.1.1 Required Clinic Areas (Required)

- **Interview areas or rooms:** These should be convenient, private, attractive, and well-lit rooms or cubicles used for conducting individual interviews with the participants.
- **Classroom:** This should be a large, attractive area (comfortable for 20 people) for teaching and facilitating group sessions for the First Screening Visit (SV1) and intervention group sessions, conducting CC staff meetings, accommodating mass-mailing operations, and for use in any other activity where a large room is needed. All cooking supplies and a sink should be located either nearby or in the classroom.
- **Participant file area:** This must be a secure area. Any material that is identified with a participant's name should be locked or in a secure area when not in use to maintain confidentiality of records.
- **Medication storage area:** This should be a secure room with space for unpacking and packing shipments of medications, holding the pill scale, and storing supplies of Hormone Replacement Therapy (HRT) and Calcium/Vitamin D (CaD) medications (shelving to hold approximately 20 boxes about 1½' wide x 1' deep x 6" high). See *Section 15.2 - Medication Storage Area* for a more detailed description of the area.
- **Blood drawing area:** This should be convenient to the CC area and include a blood drawing chair, standard blood drawing equipment, and a sink in accordance with Occupational Safety and Health Administration (OSHA) requirements.
- **Blood processing area:** This should be convenient to the CC area. It must have a sink and work counter, and a refrigerated centrifuge. Access to a -70°C freezer is required to hold the sample aliquots before shipment to the specimen repository.
- **Physical measurement area:** This area should be a private area for taking height, weight, hip and waist measurements, and other physical measurements, where the participant can feel that personal information will be kept confidential. Access to a wall-mounted mirror is recommended to perform the hip and waist measurements.
- **Examination room:** This room should be set off from the other clinical areas by a door. Any windows should have blinds or curtains that can be drawn. An examination table with stirrups, at least one standing examination lamp, a stool, an overhanging equipment table, and a sink should be available in the room. Additionally, storage space in this room for gowns, sheets, gloves, specula, lubricant, and other supplies would be desirable.
- **LAN file server space:** The file server is mounted in a floor-standing cabinet and weighs about 300 lbs. The cabinet is approximately 2½' x 2½' wide and 4' tall, requiring 6" of clearance on each side when the cabinet is closed, and sufficient clearance to open and work on both front and back. It also needs 2' of air space above the cabinet. It will generate about 500 BTUs per hour, so the space must have sufficient ventilation to disperse this heat. The file server and -70°C freezer should not be located in the same area. It must be located in a secure area to avoid use by unauthorized people or accidental shut down.

2.1.1.2 Recommended Clinic Areas

The following list includes additional specific areas likely to be needed at each CC to perform the activities for the WHI.

- **Accessible parking:** This is an important convenience for the participant that can improve participant adherence. The CC is encouraged to reimburse participants if free parking is not available.

- **Waiting room:** This should be a convenient and attractive area, with an adjacent reception area for appointment scheduling. The area could also be used by participants to complete any self-administered questionnaires on-site.
- **Reception desk area:** This area should be in or near the waiting room area.
- **Coffee area:** This area might include a small table, coffee pot, cups, coffee and tea supplies, and snacks for post-blood draw participants. Preferably, this area could be located near the waiting room. If the coffee and post-blood draw snacks must be kept in the waiting room, be sure that there are clear, understandable instructions posted for pre-blood draw participants to not have anything to eat or drink until after their blood has been drawn.
- **Telephone recruitment area:** This area should have a chair and small desk accommodations for telephoning and screening potential participants. It should be located in a quiet area away from the reception and waiting room areas.

2.1.2 Computing

2.1.2.1 Preparing Facilities for WHI Computing System (Required)

Clinical Centers must arrange for appropriate cabling of their facilities for local area network (LAN) access to each station. Contact the Clinical Coordinating Center (CCC) for cabling information.

2.1.2.2 Guidelines for Allocating Computers to Clinical Center Areas

The five personal computers (PCs) may be located throughout the CC in order to automate tasks and facilitate data management. Each CC will need to determine the most useful configuration for their CC layout. A general recommendation based on assumed tasks is provided.

Table 2.1
Suggested Personal Computer (PC) Locations

# of PCs	Station	Likely Tasks
1	Reception	Data Entry Office Automation
1	Interviewer	Current Medication Inventory Office Automation Data Entry Eligibility Determination Randomization
2	Data Entry	Data Entry and Scanning Eligibility Determination Randomization Database Reporting Office Automation
1	Near Study Pills	Study Pill Inventory Study Pill Dispensing Study Pill Adherence Data Entry

2.1.2.3 Guidelines for Data Entry Area

- **Data entry room:** The computer area should be well-lit and well-ventilated, preferably in a separate office. Since computers generate heat, they should not be in a cramped, windowless cubbyhole. Data entry preferably should not be performed in the reception area or busy office area.
- **Work space:** The table or desk that the computer is on should be large enough to accommodate a generous workspace (for forms, a copyholder, etc.).
- **Workstation:** The keyboard and monitor should be at the proper height. An operator's arms should be bent at a 90° angle when typing. If the table is too high, there are many products available that lower the keyboard. In addition, the monitor should be at eye level. If the table is too low, a stand can be used to raise the monitor or a "CRT valet" to lift the monitor totally off the desk and position it at an appropriate height. Some of these aids come with copyholders that may make data entry work easier and faster. Most computer supply companies have free trial periods for these types of equipment.
- **Ergonomic chair:** Data entry staff should have a comfortable chair. Back fatigue is a major complaint of computer users. The height should be adjustable, and the back should tilt. Before buying any furniture, if at all possible, ask staff to try it out personally since everyone's needs and preferences are different.
- **Glare-reducing screen:** Another common complaint of computer users is screen glare. There are many glare-reducing screens available that help with this problem. You can also try adjusting room lighting and positioning the screen so that it doesn't face the sun.
- **Printer table:** Laser printer control buttons should be within easy reach. There should be an adequate storage area for paper, labels and toner cartridges.
- **Computer cleaning supplies:** There are numerous cleaning products available, both for the screen and the floppy disc drives. They are a good investment, not only to increase the life of the machine, but to maintain operator comfort.
- **Personal Computer (PC) locking device:** Each PC should have a security device that locks it to the desk or table.
- **Surge protector:** Each PC should have a surge protector.

See *Vol. 5 - Data System, Section 1 - Overview* for additional guidelines.

2.1.3 Remote Sites

Procedures for screening visits, randomizations, and follow-up visits were initially developed with the assumption that participants would come to main (or satellite) CC sites for these visits and that CC staff would have access to WHILMA. (A satellite site is a site with access to WHILMA.) However, for those situations where screening and follow-up visits are conducted at remote sites without access to WHILMA, CCs must follow the required procedures as outlined in the WHI Manuals for all tests and data collection activities. Procedures and tests performed at remote locations must be performed in the same way as those at the main (or satellite) CC.

- The physical measurement of weight must be done using the same type of scale.
- The physical measurement of height must be done using the same type of stadiometer or the CC has completed a CCC approved reliability testing to use a portable stadiometer.
- ECGs must be done using the same MacPC.
- Functional status measurements must be done using the same type of hand-grip dynamometer.
- Blood drawing must be done with the same type of standard blood collection tubes.

- Blood and urine samples must be processed using similar equipment (i.e., refrigerated centrifuge) and following the same time limits. They must also be frozen in a -70° C freezer following the same time limits as those specified in Vol. 2, *Section 11 - Blood Collection, Processing and Shipment*.
- Pill weighing must use the same type of Ohaus scale and calibration weights.

Before conducting remote site randomizations and/or follow-up visits, CCs must develop a detailed plan of the procedures they plan to use and submit this plan to their CCC Clinic Manager (CM) liaison for review before proceeding. Clinical Centers should also submit information on remote site plans to the Project Office of the National Institutes of Health (NIH) and the appropriate Internal Review Board (IRB). The plan should include information such as:

- Name, address, and phone number of remote site.
- Distance from the main (or satellite) CC.
- Method of communication with main CC.
- How the remote site is staffed.
- Description of the facilities, including signage, parking, access to secured storage, phone and FAX, VCR, running water, dedicated or shared space, and other needed facilities.
- How participants attending the remote site can contact CC staff.
- Length of time the remote site will be used, with a statement of commitment from the remote site.
- Hours of operation.
- Type of visits that will be held at the remote site (e.g., screening visits, follow-up visits, Dietary Modification [DM] Intervention sessions).
- Equipment to be used.
- How participants attending only remote sites are identified.
- Handling of participant files and transportation of the files between the main CC and remote sites (CCs should maintain a complete participant file at the main CC).
- Procedures used to ensure timely data entry of screening and follow-up data.
- Randomization procedures used.

The plan must include procedures that ensure activities are performed by certified WHI staff. CCC Quality Assurance (QA) staff may include visits to remote sites during routine QA Visits to the main CC.

2.1.3.1 Remote Site Randomizations

There are 2 options for randomizations at remote sites. The first is to complete all necessary activities at the SV3, bring the forms back to the main site at the end of the day, key-enter the information and perform the randomization. The second is to fax all completed forms to the main site during the participant visit, and randomize the participant from the main site. For each instance, HRT participants must be mailed study pills within one working day (refer to *Section 4.6.3.5 - Remote Site Randomizations* for more detailed instructions).

2.1.3.2 Remote Site Follow-up Visits

Procedures and tests for follow-up visits performed at remote locations must be performed in the same way as those at the main (or satellite) CC. Conducting follow-up visits at remote site locations generally pose additional efforts by CC staff to allow for efficient data flow between the main CC and the remote site location. A CC with a remote site location should organize the activities of each to allow for accurate and timely data collection consistent with same at the main (or satellite) site. Before conducting remote site follow-up visits, CCs must develop a detailed plan of the procedures they plan to use and submit this plan to their CCC Clinic Manager (CM) liaison for review. See *Section 2.1.3 – Remote Sites* for suggested

information to be included in the plan's description. Since the dispensation of study pills is dependent on WHILMA, the procedures for how to dispense study pills in a timely manner is a challenge. Options for dispensing study pills to participants at remote site locations are described in *Section 15.4.7 – Selecting and Dispensing Study Pills for Remote Site Locations (Required).*

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2.2 Services (Required)

Clinical Centers need to make arrangements for the following ongoing services:

- **Local lab analysis** of WBC, hematocrit, platelet count, and triglycerides: It may be more cost effective to order an entire CBC from a local laboratory than to order the individual hematology tests. Frequently the local laboratory will also supply the blood drawing supplies (needles, tubes, Band-Aids, etc.) at no additional cost.
- **Local reading of Pap smear and endometrial aspiration slides**.
- **Pick up or delivery service for local blood and pathological specimens:** Many local labs will provide this service.
- **Mammography and transvaginal uterine ultrasounds:** The services used for mammography and other screening procedures should be convenient for the participants. Plans for services needed for follow-up visits should be carefully worked out at each CC.
- **Dry ice:** Monthly delivery of dry ice nuggets will be needed for shipment of frozen blood/urine samples to the specimen repository.
- **Express mail:** McKesson BioServices will supply each CC with Federal Express mailers for the monthly shipment of frozen blood and urine samples (for bone densitometry sites) to the specimen repository and for overnight shipment of endometrial aspiration slides to the central pathologist.
- **Hazardous waste disposal:** Make arrangements for disposal of contaminated supplies such as blood drawing and processing waste according to OSHA and local institution regulations.
- **Autoclave services:** Make arrangements for sterilization of the endometrial aspiration equipment (e.g., tenacula) or other non-disposable supplies or provide accommodations for an autoclave on-site.
- **Emergency services:** Make arrangements for advanced cardiac life support services. Some CCs will arrange for code team services with their clinical facility. Other CCs will stipulate that Emergency Medical Systems (911) should be contacted in an emergency. Some CCs may be required by their clinical facility to maintain emergency supplies and equipment (e.g., crash cart) on-site.

2.3 Equipment and Supplies

2.3.1 Equipment and Supplies Supplied to CCs

2.3.1.1 Equipment Supplied by NIH

- OHAUS electronic balance scale and 500 and 1,000 gm calibration weights.

2.3.1.2 Supplies Provided by the CCC

The CCC provides each CC with the following supplies. CCs order additional numbers of items marked with an asterisk (*) as needed using *Form 172 - Supplies Order* in *Vol. 3 - Forms* on a quarterly basis. Those items marked with 2 asterisks (**) are supplied for a limited time or as appropriate.

- WHI Manuals, *Vol. 1 - 8.*
- All WHI data collection forms from the Government Printing Office (GPO). See *Vol. 3 - Forms* for a list of printed forms and *Form 170 - Forms Order* for more information about ordering forms.
- Videos.
  - WHI Consent Video.
  - HRT Consent Video (optional).
  - DM Consent Video (optional).
  - HRT Training Video: Endometrial aspiration (for clinic practitioners, not participants).
  - DM Training Video: "Keeping Track of What You Eat" (English and Spanish versions).
  - List of BSE videos CCs can order.
  - Recruitment Video.
  - Recruitment PSAs (video and audio)
- WHI slide set for professional presentations (along with paper copy).
- Printed materials.
  - Recruitment brochures (for use at CC option).*
  - Recruitment print PSA.
  - Exercise brochure.*
  - Newsletters.
    - CT Newsletter.
    - DM Intervention Newsletter.
  - Hormone show card (for use with *Form 43 - Hormone Use*).
  - Lipemic serum sample photographs (for use in blood processing).
  - Participant birthday cards.*
  - USDA/DHHS Dietary Guidelines.*
- Electronic materials. (See list in *Vol. 7 - QA, Section 2.3.3 - Electronic Files*.)
  - Model consent forms (in WORD).
  - WHI logo and catch phrase (in WORD).
  - Randomization Follow-Up Planning Spreadsheet (in Excel).

- CC Quarterly Technical Report (in Excel).
- Sample documents in *Appendix E - Model CC Printed Materials* (in WORD).

- Retention aids.
  - WHI participant folders*
  - WHI magnets.*
  - WHI lapel pins.
  - WHI medication bags.*
  - Additional incentives (a new one each year).*
- WHI 7-day pill organizers.*
- Breast models for breast self-exam (ordered through CCC).
- Tape measure (in centimeters).**
- Dietary Assessment materials.
  - Food models (1 set).**
  - Measuring cups.**
  - Measuring spoons.
- DM Intervention materials.
  - Participant Manual-binder and tabs.*
  - Participant Manual-DM Intervention session materials.*
  - Your New Eating Style post-randomization booklet.*
  - Fat Counter.*
  - Food Diary.*
  - Fat Scan.*
  - Food models (butter pats for Session 1 demonstration).*
  - Pocket calculator.*

2.3.1.3 Supplies Provided by McKesson BioServices

- All HRT and CaD study pills, open-label pills, and appropriate placebos in labeled bottles. All HRT and CaD study pills come with child resistant caps (with embedded non-child resistant caps).
- The following blood and urine collection, packing, and shipping materials
  - Blood sample label sets with barcodes.
  - Urine sample label sets with barcodes (Bone Density sites only).
  - Cryogenic vials with externally threaded cap, 2 ml.
  - Freezer boxes with dividers and labels.
  - Preprinted Federal Express labels.
  - Insulated styrofoam shipping container.
  - Fiberboard shipping boxes.
  - Plastic bags, 1 quart and 1 gallon size.

- Mailing labels*:
  - Consignee address label.
  - Black-and-white class "9" label.
  - Priority overnight label.
  - "Keep Frozen" label.
  - Diagnostic specimen label .

2.3.1.4 Supplies Provided by EPICARE

- EPICARE's training video
- Heart Square (Heartware Inc.)** (1 per CC, CCs are responsible for purchasing replacements)

2.3.1.5 Supplies Provided by Businesses or Corporations

Clinical Centers may accept (and solicit) corporate support (to provide refreshments at SV0, incentive gifts, space, or video services, for example), but such support must be provided without sponsor acknowledgment. Per the NIH Project Office, donated samples may be provided if it is made clear to the donor (preferably in writing) that acceptance of the donation does not imply NIH or WHI endorsement of the product or company, and that recipients are similarly made aware either verbally or in writing.

2.3.2 Equipment and Supplies CCs Must Purchase (Required)

2.3.2.1 Computer Equipment and Supplies

- All computer equipment and supplies listed in Schedule 1A of contract.
- Laser toner cartridges.

2.3.2.2 DM Intervention

Furniture for DM Intervention group meetings:

- Tables, 36" x 72" (3-4).
- Chairs (20).
- Coffee service cart or table.

Equipment and supplies for teaching DM Intervention groups:

- Refrigerator with separate freezer section, (full size recommended) separate from refrigerator required for blood storage.
- Refrigerator thermometer.
- Coffee maker, 24-36 cup size (1).
- Electric skillet, 12" (2).
- Cooler for food transportation.
- Microwave oven (600 - 700 watt), large enough to hold one 13" x 9" Pyrex pan or stove/oven combination.
- Cart for microwave oven. (1)
- Portable easel and pads.

- Blackboard or white board.
- Erasers for chalkboard or white board.
- Dry erase markers or chalk.
- Extension cords, 12-15 feet long, heavy duty (2)
- Adapters, grounding. (2)
- Large serving platters. (2)
- Quart casserole dishes. (2)
- Baskets with liners. (4)
- Bowls with lids. (2)
- Knives. (2)
- Larger serving spoons. (2)
- Serving forks. (2)
- Cutting boards. (2)
- Server or spatula. (2)
- Pitchers, gallon or two quart sizes. (2)
- Glass Pyrex pans, 13" x 9" size. (4)
- Glass Pyrex pans, 8" square size. (2)
- Rubber scrapers. (2)
- Paper plates (8" and 4" diameter).
- Plastic silverware: knives, forks and spoons.
- Paper goods: napkins, paper towels.
- Cups, 4-6 oz. size, (hot and cold).
- Stir sticks for coffee.
- Small individual packets of sugar and non-dairy creamer.

2.3.2.3 Clinical Measurement

- Conventional mercury sphygmomanometer. It is advisable to have an additional conventional mercury sphygmomanometer and standard stethoscope available in the CC in case of an equipment failure.
- Standard stethoscope and ear pieces with bell (Littman is suggested); tubing to be a maximum of 14 inches long
- Blood pressure cuffs (small, regular, large, thigh)

- Foot stools (one to use during height measurements, one to assist participants onto the ECG table, and one for the Clinic Practitioner to use during pelvic exams)
- Balance Beam Scale - A Detecto Balance Beam Scale, Model #2391 or 339 is recommended. Detecto may be contacted at 1-800-641-2008. If the CC uses another type of scale, send the scale specifications, such as model name, model number, and local calibration services to the CCC. The CCC must approve any equipment substitutions (see *Vol. 2, Section 9.4.5 – Portable Scales)*.
- Wall-mounted stadiometer with a perpendicular polycarbonate sliding head piece and "read-here" mark that measures from 64 to 211 centimeters (25" to 84"). The Perspective Enterprises Stature Board (#PE-WM-60-84-PC meets this requirement. Perspective Enterprises may be contacted at 1-800-323-7452. If you have alternative or modified equipment, send specifications to your CCC CM contact liaison for approval. Bone density sites should use a Harpenden stadiometer (see *Vol. 6 - DXA Quality Assurance Manual*).
- Jamar hydraulic hand dynamometer, model 1 (#PC5030J1), that registers maximum kg of force during a trial with adjustable hand grip set at the second setting. (The CCC has a dynamometer to loan out if needed.) The Dynamometer may be purchased from Samons Preston, Inc. (#5030J1) at 1-800-631-7277 or Lafayette Instrument (#700105) at 1-800-428-7545.
- Calibration weights (5- and 15-kg weights or 5- and 20-kg weights). If the weights used are not certified calibration weights, have their exact weight determined by the local Department of Weights and Measures or a certified scale technician. If kg weights cannot be located, pound weights may be substituted.
- Wide Velcro straps for calibration of dynamometer
- Standard armless, straight-backed chair (such as a plastic-molded chair) approximately 45 cm high at the front edge and 38 cm deep. The seat should not be padded and should incline no more than a few degrees from front to back. A thin strip of masking tape should be placed across the seat of the chair half-way between the front and back of the seat.
- Masking tape.
- Stopwatch.
- Sheets.
- Disposable latex gloves – various sizes.
- Disposable specula in varying sizes (metal specula may be used if autoclave services are available).
- Water-soluble lubricant, such as K-Y Jelly.
- Betadine.
- Tenacula.
- Floor-standing exam light or other light source for vaginal exam.
- Exam table with slide-out step and stirrups.
- Flexible endometrial aspiration equipment.
- Scissors to cut off tip of aspirator.
- Large Q-tips for swabbing or ring forceps and cotton balls.
- Contaminated waste bags (red bags).
- Contaminated needle container (for needles and cytobrush).
- Non-steroidal anti-inflammatory oral medication (per CC consulting gynecologist choice).
- Hurricane gel (20% benzocaine) topical anesthetic.
- Gowns.

- Wooden spatulas for Pap smear.
- Cytology brush for Pap smear.

Some of these may be provided by the CC local lab:

- Glass slides with frosted ends.
- Preservative for endometrial biopsy.
- Containers for endometrial biopsy.
- Pap fixative.
- Slide mailers.

2.3.2.4 ECG Measurements

- G.E. Medical Systems Information Technology (GEMSIT) (1-800-858-7044) MACPC personal cardiograph (made as joint purchase through the EPICARE or CCC) with MACPC Instruction Manual, instruction video, 12 lead ECG Acquisition Module, and Power Module supplied by GEMSIT.
- Telephone wall plug connection.
- ECG paper.
- Adult disposable electrodes (10 per participant). Economical disposable electrodes can be ordered from LecTec Corporation:

  Electrode Type: Tracets MP3000.
  Address: LecTec Corporation
  10701 Red Circle Drive
  Minnetonka, MN 55343
  1-800-777-2291

- Step stool.
- Isopropyl alcohol (for skin preparation).
- 4x4 gauze pads or sandpaper wipe (for skin preparation).
- Felt tip markers and wax cosmetic pencils (light for dark skin and dark for light skin).
- Paper tape with dispenser.
- Scissors.

2.3.2.5 Blood and Urine Collection, Processing, and Shipment

The list below includes guidelines for blood collection, processing, and shipment supplies. You may choose to use a different vendor than the one recommended. Please note that blood collection supplies may now be ordered through McKesson Bioservices, as indicated.

Blood and Urine Collection	Recommended Vendor/Part Number:
• Needles, 21 gauge, 1 to 1½" multiple sample vacutainer.	Local medical supply
• 23-gauge butterfly with 12" tubing with multiple sample Luer adapter.	Local medical supply
• Syringes.	
• Monojet hypodermic needle (21-23 gauge, 1 ½").	
• Blood draw workstation.	Recommended Baxter S9267-1
• Royal blue-stoppered serum tubes for trace elements, no additive, silicone coated, 7 ml (*Note:* 7 ml will be printed on label in red ink; be sure you use the tubes with 7 ml in red and not 7 ml in green).	McKesson or BD 367737 (Baxter B2951-107, vacutainer tubes with hemoguard closure) or BD 6526 (Baxter B3007-54)
• Blue-stoppered tubes with 3.8% sodium citrate, 4.5 ml (sodium citrate 18 mg, citric acid 2.4 mg).	McKesson or Monoject 340478 or Terumo Venoject T206SWY (Baxter B3048-81 or Laboratory Supply)
• Lavender-stoppered plasma tubes, with powdered EDTA (Sodium (Na_2) not potassium (K_3), EDTA), 10 ml.	McKesson or Monoject 310745 Terumo Venoject T200SQ (Baxter B3042-54 or Laboratory Supply).
• Lavender-stoppered plasma tubes, with liquid or powdered EDTA (as preferred by local lab).	Local laboratory performing tests for CC
• Vacutainer holder.	Local medical supply
• Test tube racks.	Local medical supply
• Alcohol swabs or cotton balls, alcohol, and alcohol dispenser or gauze swabs.	Local medical supply
• Bandages ("Band-Aids") or surgical tape.	Local medical supply
• Biohazard container for needles ("sharps" container).	Local medical supply
• Biohazard container for waste.	Local medical supply
• Wash bottle.	Local medical supply
• Lab coat.	Local medical supply
• Disposable latex gloves.	Local medical supply
• Chlorine bleach.	Local store
• Anti-bacterial hand soap.	Local store
• Aluminum foil or yellow plastic sleeves to protect the blood drawn in the royal blood collection tubes from light.	Local store

Blood and Urine Processing	Recommended Vendor/Part Number:
• Fluid-resistant lab coat.	Local medical supply
• Refrigerated centrifuge with swinging buckets (able to reach relative centrifugal force of 1,300 xg).	Local medical supply
• Factory certified low temperature thermometer, -90°C to +20°C or thermistor.	
• Large and small test tube racks for holding vacutainer tubes and cryovials.	Local medical supply
• Disposable latex gloves.	Local medical supply
• Chlorine bleach .	Local medical supply
• Goggles or glasses or mask with face shield or barrier shield behind which to process blood samples.	Local medical supply
• Tape.	Local store
• 1 ml adjustable automatic pipettor.	Local medical supply
• Disposable pipette tips.	Local medical supply
• 10 x 75 mm or larger test tube or 15 ml conical centrifuge tube to recentrifuge samples.	Baxter C3902-4
• Sterile specimen container for collecting urine (in bone density CCs).	Baxter U3031-31
• 15 ml conical centrifuge tube with lid (in bone density CCs).	

Blood and Urine Storage and Shipment	Recommended Vendor/Part Number:
• Freezer at 70°C or colder, with CO2 back-up system and temperature recorder.	Local medical supply
• Factory certified low temperature thermometer, -90°C to +20° C or thermistor.	EverReady thermometer ULF0105 Telephone: (800) 453-7826
• Newspaper (for packing).	
• Freezer alarm for each -70°C freezer.	Rees Scientific/Informer 2400 Telephone: (800) 327-3141
• Waterproof packing tape (strapping tape).	
• Dry ice nuggets.	
• Freezer gloves/vinyl or latex rubber gloves.	
• Return address label (printed at CC).	
• Indelible ink pen.	
• Shipping tape.	
• Scale for weighing shipment.	

2.3.2.6 Other Equipment and Supplies

- Color TV and VHS VCR.
- Fax machine.
- Phone with voice mail or answering machine.
- #2 pencils for use with mark-sense forms.
- Health Education pamphlets (available if CCs choose to use them.)

  The following are WHI approved pamphlets CCs can order by calling 1-800-4-CANCER. You are only allowed to place one order per brochure per month. The maximum allowable number you can order varies from brochure to brochure. The range is from 50-200.

Approved Pamphlets	**NIH Publication Number**
• The Pap Test: It Can Save Your Life	92-3213
• Clearing the Air: A Guide to Quitting Smoking	92-1647
• Breast Exams (Spanish): Lo Que Usted Debe Saber Sobre Los Examenes De Los Senos	92-2000S
• Pap Test (Spanish): Hagase La Prueba Pap Hagal Hoy O Por Su Salud Y Su Familia	92-3211S
• Smoking (Spanish & English): Smoking: Facts and Quitting Tips for Hispanics	92-3405S
• Understand Breast Changes: A Health Guide for All Women (this is quite a lengthy pamphlet - it would probably be more appropriate for use in clinic waiting rooms rather than as a hand-out)	93-3536

Because pamphlets sometimes go out of print and are no longer available through the NCI, a few additional pamphlets have been added to the list. These are:

Approved Pamphlets	**NIH Publication Number**
• Having a Pelvic Exam and Pap Test	95-3416
• Are You Age 50 or Over? A Mammogram Could Save Your Life	94-3418
• Get a New Attitude About Cancer: A Guide For Black Americans	93-3412
Designed for Spanish-speaking women:	
• La Prueba Pap (Spanish Pap Test)	93-2694S
• Un Mamogram Podria Salvarle La Vida (Spanish mammogram)	94-3418S

2.3.3 Recommended Supplies

Waiting Room

- Pamphlets such as information brochures and WHI Interest Surveys.
- Phone books.
- Magazines or other WHI - appropriate reading material, e.g., travel, crafts, or sports publications. Magazines displayed in the waiting room should be neutral in content and should not contain articles promoting diet changes or hormone use.

Reception Area

- Shelving.
- Bulletin board.
- Calendar with dates at least six months in advance.
- Typewriter.
- Appointment book with dates at least six months in advance or access to a PC if scheduling is done via computer.
- Copier, or convenient access to one.
- Postage.
- Calculator.
- Rubber stamp with CC address.
- Shelf or hanger for coats.
- Extra pens and pencils.

Coffee Area

- Snacks for post blood draw participants.
- Plastic knives and spoons.
- Cups for hot and cold liquids.
- Water, coffee, decaf coffee, tea, sugar, sweetener, non-dairy creamer, stirrers.
- Coffee maker.
- Carafes for hot water, coffee and cold water.
- Napkins.
- Waste paper basket.

DM Intervention Sessions

- Food thermometer.
- Warming trays. (2)
- Small toaster oven. (1)
- Small tape recorder.
- Overhead projector.

- Name tags.
- Pencils and pens.
- Writing pads.
- Paper clips.
- Transparencies.
- Reference books or dietary newsletters.
- Children's toys (crayons, coloring books, reading books, etc.).

Clinical Measurements

- BSE video.
- Office supplies as needed.
- 1% lidocaine.
- 20-gauge spinal needles or comparable paracervical equipment of choice.
- 5-cc syringes or comparable paracervical equipment of choice.
- Sterile towels (disposable).
- Exam table paper.
- Exam table pillow.
- Paper pillow cover.
- Over-hanging equipment table.
- Resuscitation equipment (code cart).
- WD40 or comparable lubricant.
- Biohazard container for contaminated waste.
- Garbage can for paper waste.
- Silver nitrate sticks (to stop bleeding from tenacula puncture sites).
- Wall-mounted mirror.
- Dish detergent.
- Small lacrimal duct probe.

ECG Measurements

- Baby oil, body cream (unscented) (Use only after ECG recording if skin is irritated.)
- Dish detergent: one part detergent to 10 parts water (for cleaning Heart Square).
- Small pliers.
- Three-way adapter.
- Extension cord.
- Mattress pad.

- Towel.
- Electrodes.
- Alcohol swabs.
- Fine sandpaper wipes.

Blood Collection, Processing, and Shipment	Usual Vendor
• Paper towel dispenser.	Local store
• Timer.	Local medical supply
• Plastic disposable transfer pipettes with bulb reservoir (5-6 per participant).	Local medical supply
• Applicator sticks.	Local medical supply
• Wet ice.	Local supplier
• 3 ring binder for log sheets.	Local store
• First aid kit.	Local medical supply
• Smelling salts/amyl nitrate poppers.	Local medical supply

Study Pill Storage Area:

- Table.
- Mailers - padded adhesive.
- Filament tape.
- Clerical supplies.

2.4 Staffing

The number of staff positions at a CC depends largely on the configuration of the CC. In general, each CC has duties that can be divided into the seven following categories: Clinical Center Management, Clerical and Support, Recruitment and Interview Activities, Data Coordination and Management, Clinical, Nutritional, and Outcomes. The general responsibilities of each category are described below. In the interests of cost containment and maximum flexibility, CCs may hire part-time staff and cross-train staff to accomplish a variety of responsibilities. Clinical Centers may also utilize students, participants, and volunteers as appropriate.

Certain guidelines must be followed when using students, volunteers, and study participants to assist with CC operations. Volunteers and students must be trained for all standardized WHI tasks that they perform (e.g., consents, data collection, or data entry.) The signing of a confidentiality statement is recommended. While the CCC strongly discourages using WHI participants as volunteers (particularly CT participants), there are no "rules" against this. However, activities performed by participants must be monitored closely. Participants must be trained and certified to perform all standardized tasks like any other staff member. Participants who assist in the CC, however, must not have access to materials, records, or lead staff support beyond what would be routine for other CT or OS participants. If the participant will be interacting with other participants she should not disclose that she is a WHI participant or has had experience with screening visits or a certain arm of the study trial. Additionally, a CT or OS participant cannot attend any DM intervention sessions.

The following tasks are not necessarily assumed by one CC staff member within an area. In fact, the key areas below include tasks that are at multiple levels of responsibility and expertise.

2.4.1 Clinical Center Management

High level of responsibility and expertise

- Manage CC facilities, operations, and administrative details.
- Supervise CC personnel and staffing, particularly reception and clerical staff.
- Oversee CC flow.
- Prepare administrative, budget, and progress reports as well as cost estimates, plans, and projections for future needs.
- Communicate with CC PI and serve as administrative contact person for CCC.
- Interpret and implement protocol policies and procedures.
- Participate in regular conference calls.
- Manage medication area.

Moderate level of responsibility and expertise

- Maintain documentation for all CC operations.
- Maintain updated IRB records.

2.4.2 Clerical and Support

Moderate level of responsibility and expertise

- Schedule outside tests.
- Schedule CC visits and provide reminders (via phone and/or mail) to participants.
- Retrieve, prepare, distribute and refile participant charts before and after CC visits.

- Maintain study manuals, including updates on the WHI Manuals.
- Serve as receptionist to people entering the CC.
- Screen CC phone calls.
- Maintain appointment calendar and logs related to CC flow.
- Maintain supplies and inventory including study forms and supplies from the CCC and study pill inventory.

Low level of responsibility and expertise

- File CC documents.
- Perform mass mailings for recruitment.
- Prepare participants' informational packets.
- Carry out copying and typing requests.
- Perform word processing and correspondence.

2.4.3 Recruitment Activities

High level of responsibility and expertise

- Plan, implement, and monitor participant recruitment and retention procedures in conjunction with scientific staff and CCC.
- Establish community contacts and resources for recruitment.
- Develop CC-specific recruitment materials.
- Participate in monthly conference calls.
- Train recruitment staff.

Moderate level of responsibility and expertise

- Recruit and screen participants into the study through telephone interviews with interested respondents.
- Re-establish contact with participants lost to follow-up by telephone contacts and updating personal contact information.
- Obtain informed consent.
- Explain forms.

Low level of responsibility and expertise

- Schedule women for their screening visits.
- Schedule participants in the CT and OS for appropriate follow-up visits.

2.4.4 Clinical

The licensure requirements for performing some clinical procedures depend on individual state requirements and therefore, will be CC-specific. Consult your state practice guidelines.

High level of responsibility and expertise

- Oversee clinical assessment and intervention operations and provide quality assurance.

- Conduct CC clinical staff meetings and provide continuing education opportunities.
- Provide consistent CC services and continuity to participants.
- Perform pelvic exams and Pap smears.
- Perform clinical breast exams.
- Perform endometrial aspirations.
- Perform transvaginal uterine ultrasound (in CCs with ultrasound equipment).
- Review and interpret screening and diagnostic reports (laboratory, ECG, mammography, Pap smear, endometrial aspiration, and transvaginal uterine ultrasound reports).
- Review laboratory and clinical results and findings with participants.
- Provide referral and follow-up.
- Provide consultation during the informed consent process.
- Counsel and evaluate participants for adverse signs and symptoms.
- Respond to participants' concerns about health and symptom management.
- Participate in appropriate conference calls and liaison with CCC.

Moderate level of responsibility and expertise

- Perform blood draws into appropriate specimen tubes.
- Maintain contact with participants during flow through the CC.
- Perform medication interviews.
- Perform bone densitometry (in bone density CCs: Birmgingham, Tucson, Pittsburgh).
- Obtain 12-lead electrocardiogram.
- Process blood specimens: centrifuge, aliquot, label, scan labels, store (freeze) and ship to appropriate central blood repository or local lab.
- Provide breast self-examination teaching.
- Perform study pill adherence collections and dispense study pills.
- Perform cognitive assessment interview.

Low level of responsibility and expertise

- Measure blood pressure and resting pulse rate.
- Measure height and weight.
- Measure waist and hip circumference.
- Perform functional measurements.
- Collect urine specimens (in bone density CCs).

2.4.5 Nutrition Interventionist

High level of responsibility and expertise

- Oversee nutrition assessment and intervention operations and personnel.
- Provide training and quality assurance of nutrition assessment and intervention operations.
- Participate in appropriate staff group and other related conference calls.

- Provide dietary consultation during informed consent process.
- Organize scheduling for dietary intervention groups.

Moderate level of responsibility and expertise

- Run intervention groups.
- Provide individual counseling.
- Maintain intervention and quality assurance forms.
- Maintain participant progress notes.
- Monitor dietary changes in participants and provide feedback.
- Monitor attendance and provide make-up sessions for intervention participants.
- Respond to participants' ongoing concerns about diet, food preparation or completion of forms.

Low level of responsibility and expertise

- Schedule intervention groups.
- Shop and prepare foods for intervention activities.
- Assemble intervention class materials and equipment.
- Mail class reminders for intervention sessions.

2.4.6 Dietary Assessment Staff

Moderate level of responsibility and expertise

- Teach participants about completing dietary questionnaires *(Food Frequency, Four-Day Food Record).*
- Assign dates for completion of *Four-Day Food Record.*
- Review and document *Four-Day Food Record.*
- Review *Food Frequency Questionnaire* for completeness.
- Assess participant's ability to complete dietary questionnaires as a basis for determining eligibility for dietary intervention.

2.4.7 Outcomes Specialist

High level of responsibility and expertise

- Evaluate medical records documents to determine if they are appropriate and adequate for adjudication.
- Assemble adjudication case packets.
- Coordinate activities of staff, (e.g., data coordinator, physician adjudicator) involved in processing outcomes and maintain routine systems of communication.
- Refer questions appropriately to Clinic Practitioners (serious adverse experiences or safety issues).
- Participate in monthly conference calls.
- Review ICD-9-CM codes on hospital facesheet for outcomes of interest for WHI.

Moderate level or responsibility and expertise

- Ensure participant has a current Medical Records Information release signed prior to investigation of any potential outcome.

- Review medical history and update forms to identify events that indicate a possible WHI outcome.
- Review forms for completeness and check with participant to get appropriate details of medical history and health provider contacts.
- Request documents required for an outcome investigation from external sources such as a hospital, physician's office or laboratory and request additional documentation if needed.
- Route requested outcomes adjudication case packets for central adjudication.
- Monitor and track timeliness and completeness of documents requested from external sources.

Low level of responsibility and expertise

- Maintain participant's outcome files. This includes creating new outcome charts and filing.
- Key-enter adjudicated outcomes determination into database.
- Review list of providers maintained in the WHILMA database.

2.4.8 Data Coordinator

High level of responsibility and expertise

- Serve as CC database and LAN manager
- Supervise data entry staff
- Monitor data flow at the clinical center
- Train other staff to use WHILMA
- Monitor eligibility
- Serve as CC unblinding officer
- Enter study drugs into WHILMA inventory

Moderate level of responsibility and expertise

- Participate in monthly conference calls
- Keep staff up-to-date on WHILMA changes
- Monitor data quality
- Train other staff on availability of and uses of WHILMA reports and CCC reports
- Enter nutrition intervention and outcomes data

Low level of responsibility and expertise

- Key-enter and scan study forms
- Run routine WHILMA reports

2.5 Participant Contacts

Clinical Centers should provide flexible office hours for the convenience of the participant (early mornings, weekends, and evenings). The number of weekend and evening hours may vary among CCs based on the participant population.

2.5.1 Participant Timeline (Required)

- **Recruitment and Prescreening:** Identifying and implementing the recruitment strategies take various lengths of time, depending on the recruitment source and the arrangements necessary to contact the potential participants. Clinical Centers will contact women who are interested and age-eligible, by telephone or mail, for a prescreening. Women eligible after the initial contact will be asked to come to an SV0 or an SV1. See Section 3 - Recruitment.
- **Pre-Screen Visit / Orientation (SV0):** This is a recommended visit for which women can be brought into the CC to learn about the WHI in a group format. Interested women may be given SV1-specific forms to complete prior to the SV1 visit.
- **First Screening Visit (SV1):** This visit is usually scheduled within two to three weeks of the initial contact. See *Section 4.1 - Screening Visits for WHI.* Allow adequate time between the initial contact or SV0 and the SV1 for the woman to receive and/or complete the mailed questionnaires.
- **Second Screening Visit (SV2):** This visit should usually be scheduled soon after the SV1, preferably within one week. Allow adequate time between SV1 and SV2 to obtain and review local laboratory results.
- **Third Screening Visit (SV3):** The SV3 should usually be scheduled within four to six weeks after the SV2, allowing sufficient time to get mammography and other results returned. However, if mammogram results are available by SV2, DM women could potentially return in as few as eight days after they complete *Form 62 - Four-Day Food Record*. For women enrolling in HRT, the minimum interval between SV2 and SV3 is 28 days to allow an adequate assessment of adherence to the enrollment period on HRT study pills.
- **Follow-Up:** Semi-annual contacts and annual visits should be scheduled so that the annual visit falls within the target window of the anniversary date of the woman's randomization into the CT. For HRT or CaD participants an early contact (six or four weeks, respectively, after randomization) is required to answer questions, evaluate safety and adherence, and respond to questions and concerns. See *Section 16 - Follow-Up Contacts.*

  The time interval from SV1 to SV3 must not exceed 6 months. Women not randomized to the CT within 6 months of SV1 will be required to repeat baseline measures and forms falling outside the 6-month window. *Form 2/3 - Eligibility Screen*, *Form 11 - Consent Status*, and *Form 60 - FFQ* do not need to be repeated. (See *Section 4.5.3 - Time Limits During Screening*.)

  The time window for each follow-up contact is $\pm$ 2 weeks of the target date. The target date is based on the randomization date even if a previous contact is outside the allowable window. The timing of SV3 should be scheduled to the participant's anticipated availability at that time of the year. The goal is to keep the participant on schedule as much as possible. Aim to get 90% of the contacts within $\pm$ 2 weeks of the target date and only extend the window for those participants who absolutely cannot attend follow-up visits closer to the target date.

2.5.2 Tasks Per Participant Contact (Required)

The forms recommended for screening contacts and required at follow-up contacts are shown in *Vol. 1, Table 1-A1.1 - Frequency of Data Collection.* Clinical Centers have the option to rearrange the activities to earlier or later screening visits to better fit the flow of the particular CC, as long as the arrangements meet the specific requirements given in *Section 4.1 - Screening Visits for WHI*. Additionally, no procedures or data collection may be done until the participant has signed the appropriate consent form.

2.5.3 Estimating Number of Participant Contacts

Each CC manages its own workload of recruitment, screening and follow-up contacts. The "Randomization Follow-Up Planning" spreadsheet is a tool that CCs can use to estimate the number of monthly randomizations and corresponding number of screening visits needed to meet the recruitment goals. A CC-specific Randomization Follow-Up Planning Spreadsheet has been sent via eMail from the CCC to each CC. The spreadsheet is also useful in estimating the number of follow-up visits resulting from the randomizations. In using the Randomization Follow-Up Planning Spreadsheet, you may find it helpful to initially determine the number of randomizations and enrollment visits needed to be conducted per month. Then, you can work backwards to determine the number of screening visits per month and work forward to determine the number of follow-up visits per month your CC can expect. A recent addition to the spreadsheet is a graph that plots the number of visits per month each CC can expect during the course of the study. The graph is generated by data from the spreadsheet and will reflect any changes made to the spreadsheet.

It is recommended that each CC update this spreadsheet on a regular basis (e.g., monthly) to continuously monitor your CC's space and staffing needs. See *Figure 2.1 - Projected Number of Screening Activities, Randomizations and Follow-Up Visits Per Month* for an example of a typical spreadsheet showing the projected number of screening and follow-up visits per month at a CC. Detailed instructions on how to update and most productively use the spreadsheet can be found in the shared drive at your CC under "Reference Guidelines for Interpreting the Randomization Follow-Up Planning Spreadsheet." Additional questions can be directed to your CCC CM liaison.

Figure 2.1
Projected Number of Screening Activities, Randomization and Follow-Up Visits Per Month

2.6 Activities Common To Participant Contacts

Each participant visit to the CC has a common flow and includes similar procedures. See *Figures 4.3, 4.5, 4.7 - Overview of SV1, SV2, and SV3*, respectively and *Section 16 - Follow-Up Contacts* for participant flow at specific visits. Activities common to CT visits include:

- Mail appointment reminders, self-administered forms and clinic location instructions one to two weeks before the scheduled visit.
- Reception.
- Review personal information.
- Review self-administered forms (by interviewer).
- Collect specimens.
- Perform clinical measurements.
- Complete visit exam.
- Dispense medications (for HRT and CaD).
- Schedule next appointment.

Activities common to Dietary Modification (DM) component visits include:

- Mail or telephone reminders.
- Reception.
- Group activity.
- Plans for next visit.

2.7 Clinical Center Checklists

It may be helpful initially to have checklists for routine tasks posted in the CC area. For example, ***Error! Reference source not found.*** - ***Error! Reference source not found.*** lists procedures that must be completed daily, weekly and monthly. The General Checklist identifies procedures that must be completed less frequently.

Figure 2.2
Clinical Center Checklists

Daily Checklist

1. Prepare classroom materials.
2. Stock the blood-drawing tray.
3. Send out appointment reminders for next week's appointments or call one to two days before the participant's scheduled visit.
4. Review lab results returned from local lab.
5. Review results returned from Pap smears, mammograms, endometrial aspirations, and transvaginal uterine ultrasounds.
6. Record freezer temperatures.
7. Stock clinical exam areas.
8. Prepare participants' files for next day.
9. Scan and key-enter forms from previous and current days.
10. File participants' files from previous day.
11. Arrange to autoclave used specula (if made of metal) and tenacula.
12. Calibrate participant weighing (Ohaus) scale.

Weekly Checklist

1. Insert WHI Bulletins and updates in all WHI Manuals within one week of receipt from the CCC.

Monthly Checklist

1. Send frozen blood samples to McKesson BioServices specimen repository.
2. Inventory CC supply of HRT and CaD study pills and order if necessary.
3. Discard returned study pills to McKesson BioServices.
4. Check stock of supplies and reorder.
5. Participate in routine conference calls (for Lead CC staff).
6. Certify internal temperatures of freezer and centrifuge with a certified thermometer.

General Checklist

1. Prepare quarterly progress reports.
2. Prepare quarterly Forms Order.
3. Prepare the annual budget renewal.
4. Complete annual IRB approval.
5. QA checks and reports (see *Vol. 7 - Quality Assurance).*

2.8 Participant Files (Required)

Each woman coming to the CC for an SV1 has a participant file labeled with the participant's WHI ID number. The participant file should contain only those materials, forms, and letters pertaining to WHI. Clinical Centers must retain records for CT and OS participants for the duration of the study.

Specific guidelines have not yet been developed to indicate the amount of time that forms should be retained after a participant has "dropped out" of the screening process (i.e., is not eligible for or declines enrollment or randomization). The number of documents that CCs can store varies depending on their facilities. However, remember that it will be common for women to be ineligible or to decline further screening and then decide to resume screening at a later date. Thus, when a participant declines further screening, it is recommended that her forms are kept reasonably accessible for at least 6 months (after which most are outdated for the purposes of screening (See *Section 4.5.3 - Time Limits During Screening*).

2.8.1 Release of Participant Files (Required)

No information from the participant's file should be released to anyone other than WHI personnel (e.g., your local CC and CCC personnel) or authorized FDA staff (for HRT and CaD participants) without the express written permission of the participant.

2.8.2 Description

The participant file should be labeled with the participant's unique WHI ID number. Use file folders that have fasteners on the side or top on both sides to secure materials in the file.

Files may be filed by participant name, but this is not recommended because records of participants with the same name may get mis-filed. A terminal-digit filing system may make handling records easier in participant file areas, particularly with a large number of records. It is best to decide on a filing system before ordering the file folders and labels.

Participant files must be kept in a secure area of the CC. The area must also be convenient and accessible to the reception or office staff.

2.8.3 Contents and Organization

All materials pertaining to a participant should be kept in the participant file. This includes the consent form(s), data forms, letters to and from the participant, phone contacts, letters to and from the participant's personal physician, notes about the participant and the participant's contact schedule.

The files may be organized in the following manner:

Left Side of File	Right Side of File
Contact Information and Correspondence (most current on top)	Exam Forms
	Questionnaires (by date with most current on top)

2.9 Clinical Center Internal Procedure Manual

It is strongly recommended that each CC develop a CC Internal Procedure Manual that includes policies and procedures specific to the individual CC. This could include topics such as:

Clinic Operations

- Facilities
  - Diagram of CC layout.
  - Days and routine hours of operation for your CC, including those that are designed to accommodate women unable to come at usual hours.
  - Location of WHI Manuals within the CC.
  - Location of FAX. Is it on-site or in another building?
  - Location of computers and printers. List of staff positions that have access.
- Supplies, Services, Equipment and Maintenance
  - Inventory and location of CC equipment. Indicate those items that are WHI-specific or dedicated.
  - Inventory of CC supplies, forms and medications.
  - Vendors and services: List of vendors for CC operations, materials and services (e.g., dry ice, hazardous waste disposal, etc.), clinical procedures materials, including examination room and lab supplies. Indicate turn-around time and minimum stock for each. See *Section* ***Error! Reference source not found. - Error! Reference source not found.*** and *Section* ***Error! Reference source not found. - Error! Reference source not found.***.
  - Maintenance resources: Include those services used for maintenance, calibration of equipment and general housekeeping. Specify name and phone number for freezer and computer maintenance and emergencies.
  - Procedure for cleaning instruments, gowns and protective cover-wear per OSHA requirements, if disposables are not used.
- Staffing (see *Section* ***Error! Reference source not found. - Error! Reference source not found.***)
  - Organization chart of CC.
  - Directory of all CC staff (including PI and Co-PIs) including location and phone numbers.
  - Job descriptions for all WHI positions.
  - Description of staffing back-up plans and personnel.

Clinic Safety and Emergency Procedures

- Plans for fire, earthquake, or other disaster occurrences, including emergency phone numbers and contacts.
- Clinical Center procedure for medical emergencies. Include copy of Incident Report Form.
- Unblinding procedure, including name and phone number of unblinding officer. Means of contact should also be included, whether by phone, pager, etc., and off hour coverage plans.
- Safety protocol for lab accident (including accidental needle puncture, and biohazardous or chemical spill). Include copy of Incident Report Form if different than above.
- After-hours contact schedule and phone numbers.

Recruitment

- Copies of all recruitment materials, including letters, bus routes, maps, information materials, interest surveys, newsletters, etc. Include all recruitment plans, calendars of recruitment activities, and strategies, and any other additional scripts if used.
- Timetable of recruitment material distribution.
- Outline of SV0 activities if SV0 is utilized.
- Systems for reviewing and responding to monthly recruitment reports sent by CCC.

Clinical Procedures

- Laboratory
  - Phlebotomy and processing procedures for CC: Internal QA system for monitoring blood drawing, urine collection and processing and shipping of specimens.
  - Local lab: Accreditation, list of tests utilized, normal value range for each test.
  - Local lab and central lab tracking procedures: Tracking of all lab results, logging system utilized. Tracking of specimen shipments.
  - Any Clinical Center-specific lab alert values beyond those in *Vol. 1, Protocol, Section 5.5 - Notifications*.
  - System for communicating results to primary care providers and participants.
- Mammography
  - List of ACR-accredited facilities in the area.
  - Result notification system and communication to primary care providers and participants.
- DM Materials Storage
  - Location of materials.
  - System for organizing, identifying and inventorying supplies.
- DM Participant Education Materials
  - Copies of all materials created by the CC that are given to DM participants.
- DM Group Formation
  - Procedures for assigning participants to DM groups including:
    1. Waiting list.
    2. Telephone log.
    3. Prioritizing participants not assigned to a group > 8 weeks postrandomization.
    4. Maintaining contacts with women waiting for groups.
  - Procedures for non-computerized group formation, if applicable.
- DM Group Scheduling
  - Procedures for scheduling DM groups.
  - Procedures for scheduling DM Group Nutritionists.
  - Procedures for contingency plans if Group Nutritionist and/or classroom are not available.

- DM Review and Assessment
    - Description of system for reminding participants of regularly scheduled monthly/quarterly sessions (e.g., postcards, letters, buddy systems, phone tree).
- DM Observation
    - Description of system used to document and follow-up issues identified via *Form 305 - Nutrition Intervention Checklist*.
    - Description of system used for coordinating facilitator observations including:
        1. Scheduling observations.
        2. Scheduling post-observation conferences.
        3. Scheduling Action Plan follow-up.
        4. Storage of completed observation forms (*Forms 70*, *71* and *72*).

Data Management

- Policies and Procedures for:
    - Maintaining log of approved changes/additions to WHI computing system.
    - Maintaining log of computer problems and inquiries.
    - Disposing (shredding) of unneeded confidential documents.
    - Backing up local workstation drives.

2.10 Emergency Procedures

Each CC should have specific procedures outlined for handling emergency situations. All emergency procedures described below are guidelines. Specific procedures can be developed at CC option. Specific requirements and strict step-wise instructions for emergencies can be fully documented in the CC Procedure Manual. Refer to *Section 15.6 - Study Pill Adherence Monitoring (Required)* for guidelines on handling situations related to study pill overdose.

2.10.1 Telephone Procedures

If a caller feels her situation is an emergency, some "on-the-spot" evaluation may be needed. If the situation clearly is not an emergency, the caller should be reassured and calmed. If the caller can be calmed, advice can then be given or the call transferred to a Clinic Practitioner or the Clinic Manager. If the caller cannot be subdued or if the situation may be deemed an emergency, the procedures outlined below should be followed.

- Inform Clinic Manager of existence of phone emergency.
- Have participant file pulled.
- Record the participant's full and correct phone number.
- Record the name of the caller if other than the participant.
- Record the address of the caller; include a cross street if possible.
- Find out if there is anyone else in the house who may assist them.
- If necessary, have someone in the CC call the local emergency number, such as "911." Keep the caller on the line until help arrives.
- Give the Emergency Medical System the CC phone number. Ask where you can call to get further information about the caller's status or condition.
- Record the encounter on the narrative sheet in the participant's file. Additionally, keep a record of emergencies in a separate file in the CC. Note on the record the participant's name, the staff member who assisted the caller, the date and time of the call, a summary of the problem, actions taken and a summary of the result.

2.10.2 Clinical Center Emergencies

- Involving a participant:

  In possible emergency situations, it is better to be overly cautious than not cautious enough. If the participant is injured or unable to leave the CC due to illness, call a person listed on the Contact Information. If a contact person cannot be located, a staff member of the CC should make every reasonable effort to get the participant to medical care. If hospitalization seems necessary, contact an ambulance or call 911 for transportation. Record the emergency and disposition in the participant's file (e.g., on an Incident Report Form) and make a copy for a separate file in the clinical area.

- Involving a staff member:

  Follow recommendations of the Health and Safety Division of your institution. Clinical Center staff should be familiar with these guidelines and copies of the guidelines should be readily available.

  Notify your Clinic Manager and PI when any emergency situation occurs.

2.10.3 After-Hours Procedures (Required)

Each CC should establish procedures by which a participant can contact CC personnel when the CC is closed. For example, a recording at the CC can direct the caller to an emergency number or the CC phone can be transferred to a person able to handle possible emergencies.

Clinical Centers are required to have a freezer alarm system that notifies designated staff if there is an after-hours freezer failure. See *Section 2.3.2.5* and *Vol. 2, Section 11 - Blood and Urine Collection, Processing and Shipment* for further details.

2.11 Interviewer Procedures

This section contains general procedures for research project interviewing of study participants. The guidelines describe the interview function and interviewing techniques, but they are intended neither as specific instructions for completing forms nor as detailed directions for conducting visits. Those instructions and directions are found in *Vol. 3 - Forms*.

These guidelines are described to assist WHI interviewers as they perform their duties in the context of participant contact. They apply to all WHI staff members eliciting information from participants.

2.11.1 Overview

As an interviewer, you are the participant's link with WHI. While you do not act alone in establishing a relationship with the participant, an unpleasant interview experience could tip the balance for a participant who is beginning to lose interest or is contemplating withdrawal.

Although in many ways the CC resembles a medical setting, it is not a medical care facility. The following characteristics distinguish WHI CCs from medical care facilities:

- WHI is a research project, and personnel who staff the CCs are part of a research team.
- Research project interviewers are not caregivers, helpers or advisors beyond the scope of the protocol.
- Individuals who take part in the study are *participants*, not patients; they join and remain voluntarily.
- Participants contribute to the content of scientific knowledge without gaining much for themselves.
- The CC does not bill participants for routine study visits.

Within the WHI research setting, you collect data on forms in three ways:

- Conduct in-person interviews to question participants for information or to verify observations with forms such as *Form 43 - Hormone Use.*
- Conduct telephone interviews using forms such as *Form 3 - Eligibility Phone Screen*.
- Review or preview participant self-administered forms with participants and summarize data items using forms such as *Form 30 - Medical History Questionnaire.*

2.11.2 Research Project Interviewing

For successful interviewing, you should have broad knowledge of the research project interview task as well as the forms and their completion. Your knowledge base should include the following:

- *Nature of research interviewing*: An interview is a social interaction designed to exchange information between a questioner and a respondent. The quality of the information exchanged depends upon the skill of the interviewer in handling that relationship.
- *Scope of research interviewing*: The research project interviewer collects data that will answer research questions.

The *research* interview contains elements that separate it from other kinds of interviewing. Strictly speaking, the research interview has the practical, utilitarian goal of data collection. In WHI, research project interviewers must combine the utilitarian objective with a more social objective of participant retention.

The retention objective is an important one, and social interaction should be a part of every interview. But it is also important that the interview not drift into lengthy conversation. Conversation of a general nature for the purpose of participant bonding should be confined to a few minutes at the beginning and the end of participant visits or phone calls.

- *Significance of research interviewing*: The research project is dependent upon the reliability and validity of the data collected by its interviewers. Bias in interviewing can compromise data.

The interviewer reduces the chance of bias by presenting neutral reactions to all answers and by maintaining a brisk, regular pace of question delivery. Regardless of how carefully worded the questions and how neutrally presented, research interviews are subject to bias from two sources: interviewer delivery and participant responses. It is the interviewer's job to minimize bias from either source.

Interviewers can introduce bias into survey results by interpreting answers, favoring one answer over another, treating some questions as sensitive, reacting to liked or disliked participant characteristics, or using slanted probes or positive or negative filler words. To avoid these potential sources of bias, interviewers must perfect both neutral delivery and neutral response.

Participants can bias their responses by trying to answer questions when they simply don't know the answers. Even when the participant knows the answers, she doesn't always give them truthfully. What's more, she often doesn't realize that she's not being truthful. The participant may bias her response unconsciously by slanting answers to make herself feel better, giving responses she thinks her friends would, or providing answers she thinks the interviewer expects. The interviewer overcomes participants' emotional, unconscious bias tendencies by presenting questions at a regular pace and by maintaining neutrality.

2.11.3 Interviewer Roles (Required)

Although the ultimate goal of the research project interview is standardized and reliable data collection, the interviewer also plays an important role as the human conduit of information from participants to the database. The way the interviewer conducts the interviews both facilitates and standardizes the gathering of the data.

The following are some of the important roles of the interviewer:

Manage the Interview

- Control and focus the interview without dominating either the exchange or the participant. Your job is to get information, not to show what you know. The participant's answers to the questions are important. You convey that importance by your professional demeanor, by maintaining control of the situation, and by focusing on the content of the interview.
- Be politely firm and businesslike; timidity signals lack of confidence. If you communicate insecurity or hesitancy to participants, some of them will take advantage and assume a power position, others will feel sympathetic and assume a "mother" position. In either case, the participant's responses could be biased. The participant assuming the power position could distort strong opinions to keep the position; the mothering participant could try to make the interviewer's job easier by answering obligingly.
- Dress for a supporting, not a starring, role in the survey scenario. Neatness and professionalism are the rule. Clinical Centers may want to provide dress codes.

Collect Data

- Understand the purpose and meaning of the data items on the forms. If you don't, ask your supervisor for clarification.
- Take no personal stake in the content of the interview. Make sure your opinions and behavior neither add to nor subtract from the research intention of any items in the forms.

Assess Symptoms

- See information on symptom assessment in the explanation of *Form 10 - HRT Management and Safety Interview* and *Form 17 - CaD Management and Safety Interview* in *Vol. 3 - Forms*.

Encourage Participation and Adherence

- Send the participant away with an overall feeling of well-being. The goal is to make the participant's CC encounters pleasant enough to be worth repeating.
- Be friendly but not chummy. Use a manner of speaking that is natural to you. If your usual manner is too casual, then with your supervisor's help, develop a firmness and modularity in this role that is genuine.
- Approach the interview with pleasure and assume the participant will do the same. Most people like being asked about themselves and their well-being; you are giving participants an opportunity to express themselves.
- Keep contact notes on personal conversation for use by the next interviewer. Record participant information that another interviewer might reasonably be expected to know, not gossipy kinds of information.
- Review contact notes before each new contact. Be careful when using comments recorded by another interviewer. There is a difference between "remembering" a participant and "talking about" a participant, which may be interpreted as a breach of confidentiality.

Present Incentives and Rewards

- Project sincerity and enthusiasm when you present participant incentives or awards. Without words you can announce a shift in mood from data collection to a presentation context by shifting your physical position toward the participant (see "Use Body Language" under *Section* ***Error! Reference source not found. - Error! Reference source not found.*** below).

Recruit New Participants

- Encourage respondents to join and remain in the study, but don't oversell or coerce. Many people will agree to participate to end a phone call and then never return materials or show up for appointments.
- Leave the door open for participants who are reluctant to participate in the study so that you can make another try at a later time.
- Emphasize the contribution that a participant alone can make if you suspect that other persons in the household are influencing the respondent's decision about enrolling.

Clarify the Nature of the Research Setting

- Make sure participants know that although in many ways the CC resembles a medical clinic, it is not a medical care facility, and you as an interviewer are not a caregiver, helper, or advisor.
- Give participants information about your role as an interviewer by making the following points:

  1) That you are a research project interviewer, not a source of primary care.

  2) That you are not in a position to diagnose or refer them to someone other than their primary care provider for further medical care.

The following is a sample explanation you can give to a participant:

"Because this is a research study, there are some similarities between our Clinical Center and your physician's office. This can create some confusion about what to expect when you come to visit us.

"We want you to know that we are not your primary care providers. While we perform some of the same procedures as your physician, we do not collect complete information on your health. Your family physician or primary care provider knows you best and can provide you with complete medical care or refer you to other physicians or specialists.

"We are concerned about you and your health, however, so we offer the following:

- *We will refer you to your family physician or primary care provider if we find something that we feel you should know about or should check more thoroughly.*
- *In the waiting room we have available pamphlets and reading materials on programs for quitting smoking, lowering your cholesterol, etc. Please feel free to take these with you."*

(*Note*: When presenting participants with abnormal blood results or other clinical problems, choose your wording carefully. Do not unnecessarily alarm the participants. Do not diagnose the problem or recommend further tests be performed. Refer the participants to their physicians.)

Represent the Clinical Center and WHI

- Always be polite. Remember, you represent the CC and your co-workers.
- Call participants by name to make the experience at the CC more personal. Always use titles (Ms., Mrs.) and last names unless the participant requests otherwise.
- Impart to the participants respect for the confidentiality of the information they provide by focusing your attention on them alone. Do not let the interview be interrupted by co-workers in a casual manner.

The telephone interviewer who conducts the initial screening phone call has an important responsibility for WHI. In most instances, the telephone interviewer's ability to develop and maintain a positive rapport with the participant influences initial recruitment, the quality of the data obtained, and the willingness of the participant to remain in the study for the duration. It is important that all interviewers maintain a professional and friendly manner at every contact with the participant.

2.11.4 Interview Guidelines

The research interview is a structured conversation designed to exchange information between a questioner and a respondent. The structure is provided by questions and scripts. The quality of the information exchanged depends upon the skill of the interviewer in handling that relationship. The following are some techniques to keep in mind as you conduct your interviews.

2.11.4.1 Interview Techniques (Required)

Use the Setting

- Use the setting to your advantage. The CC provides waiting rooms and office space for WHI interviews. The setting accomplishes two important things: it gives a professional impression and it puts the participants at ease.
- Insist on the privacy of the interview, except for observation by WHI personnel. Observers should not intrude into the interview.
- Ask family members to wait in the waiting room during the question and answer periods of the interview, even if you have allowed them to be present during the introductory parts of the interviews.

Prepare for Each Interview

- Prepare for the interview before you bring the participant in so that you can focus all of your attention on the participant. See preparation details for each contact in *Section 4 - Screening* and *Section 16 - Follow-Up Contacts.*
- Review the contact notes in the chart before beginning each contact.
- Make sure you have all the forms and materials necessary to complete the interview.
- Make sure no other participant's information is on the desk.

- Avoid interviewing someone you know. If you see the name of a friend or acquaintance among the participants, tell your supervisor.

Know the Forms Thoroughly

- Follow all instructions and suggested scripts contained on the form itself and in instructions in *Vol. 3 - Forms.* Following or not following the instructions, scripts or recommended remarks makes the difference between consistent and inconsistent data.
- Study the questions and data items on the forms so that you understand what they mean. Become familiar enough with them so that you can *ask* the questions instead of *reading* them, but don't try to ask questions from memory alone. Use the form as a reference at all times.
- Practice parts of the interviews that seem awkward or unnatural to you until you can ask the questions in a natural manner.
- Review the instructions for each form regularly. Do not rely solely on memory for detailed instructions on form use.
- Use the scripted parts of the interview as they are written. Discuss with your supervisor the content and flow of recommended remarks, especially when in doubt about appropriate procedures to follow in unusual situations. (Referral of specific problems to the CCC is the responsibility of the supervisor.)
- Use the response categories that are given. Probe for specificity if necessary (see "Probe Carefully" below).
- Avoid as much as possible using the "other" or "don't know" category.
- Never assume you know what the participant means. Probe for clarity if necessary (see "Probe Carefully" below).
- Record open-ended answers verbatim.
- Record your comments in brackets on the form if you have strong impressions about a participant's answer. Indicate the question you are referring to, and make your comments as clear and concise as possible.

Maintain Professional Contact

- Treat every participant with graciousness and respect; treat none as a buddy.
- Do not give personal opinions on any study matters and do not give advice on personal matters even if you are asked.

Set the Appropriate Pace

- Use a brisk, businesslike pace, but don't rush the participant or show impatience.
- Vary from your established pace on cues from the participant. If the participant shows frustration or lack of understanding, then slow down. If the participant shows annoyance or jumps in with answers to anticipated questions, then speed up. But do not skip questions.

Maintain a Neutral Tone

- Speak distinctly, without unusual inflection that could draw undue attention to part of a question.
- Do not place emphasis on specific response alternatives.

Maintain a Neutral Response

- Record information faithfully regardless of whether you think it's good, bad, boring, or exciting.

- Keep your reactions to yourself, no matter what you may think of an individual or the feelings expressed. Practice *not feeling* a reaction; school yourself out of emotional attachment to the information you hear.
- Inspire confidence by your detachment so that participants feel comfortable giving you the unvarnished truth.
- Do not indicate surprise, pleasure, approval, or disapproval of any answer by word or action. Do not smile, grimace, gasp, laugh, frown, agree, or disagree. Even a slight intake of breath or a raised eyebrow may indicate to a participant that you are reacting to an answer. Project smooth, gracious acceptance of information, no matter how outrageous the content.
- Repeat the question exactly as it is written if the participant misunderstands a word or a question and asks for clarification. Do not define words, interpret questions, or suggest answers. See "Lack of Understanding or Recall" in *Section* ***Error! Reference source not found. - Error! Reference source not found.*** below for how to respond if a participant does not understand a question.

Deliver the Questions Thoughtfully

- Make your delivery smooth, natural, and enthusiastic. Avoid sounding like a robot.
- Sound fresh for everyone. You may ask the same questions a dozen times in a day, but participants hear them only once in their interview.
- Use the questions, scripts, or recommended remarks as they are written, without apology.
- Emphasize that there are no right or wrong answers; the only thing that matters is the truth from the participant.
- Do not try to justify questions or to defend a line of inquiry; you are asking questions that have been asked of many other participants.
- Keep the questions in the order they're written and maintain the flow of the visit.
- Record open-ended answers in the exact words the participant uses.
- Tell your supervisor if you find a problem with the wording of a question.

Probe Carefully

Probing is a critical technique to master, as it is easy to fall prey to directing responses or altering the meaning of a question. Probes must be as uniform as possible within and among clinics.

- Use probes to elicit answers to either closed-ended or open-ended questions.
- If you feel a participant has provided an inappropriate response or doesn't understand the question, first try repeating the question and the response categories verbatim.
- Probe by asking sufficient supplemental questions to get the participant's answers in full but not so many that you don't get the truth.
- Avoid asking leading questions when probing and do not suggest an answer.
- Do not insert your own ideas of what the participant might be saying. Do not agree or disagree with an answer.

<u>Probing for answers to closed-ended questions:</u>

In closed-ended questions, the need for probing arises when the participant gives an answer that is not included in the response categories.

Example:

> The question, "Have you felt so down in the dumps that nothing could cheer you up?" (on *Form 37 - Thoughts and Feelings)* asks the participant about general depression.
>
> In reviewing the form with the participant you find that answer blank. You read the instructions and the question, and the participant says, "Well, everybody has those feelings sometimes."
>
> Repeat the response categories, "Would you say you were down or depressed: Not at all, A little, Enough to bother you, Quite a bit, Very much so, or Extremely so?"
>
> Participant: "Well, I was blue for a day or two."
>
> Ask the participant to choose the category that fits best and repeat the categories.

Probing for answers to open-ended questions:

In open-ended questions two problems call for probing: the need to *clarify* a response and the need to *get additional information* in a response.

The following are examples of neutral probes to *clarify*:

> *What do you mean by that?*
> *Why do you say that?*
> *In what way was it a problem?*
> *Could you rephrase that?*

The following are some examples of neutral probes to get *additional information*:

> *Are there other (repeat the phrase from the question)?*
> *How else would you describe (repeat the phrase from the question)?*
> *What else (repeat the phrase from the question)?*

See instructions for using *Form 3 - Eligibility Phone Screen* in *Vol. 3 - Forms* for extensive descriptions and examples of probing.

Control Silence

- Use silence at the right moment to show your patience while waiting for the participant to formulate an answer, but do not leave the silence too long or it will threaten the participant. In role playing with other interviewers, experiment with pauses to discover your own reactions to silences.

Use Body Language

- Use the setting, your posture, and your gestures to convey the feeling you wish to project to best control the interview. If you sit with a desk between you and the participant, you project formality and assume a certain amount of authority. For less formality and authority, move your chair around the desk so that you are face-to-face with the participant.
- Lean forward slightly to communicate sincerity or to focus or refocus the participant's attention on you and your questions.
- Keeping your eyes on the form with your pencil poised to write when asking questions tells the participant you are not just making conversation. Try the technique with an inattentive participant. However, be careful to convey individual interest in the participant (not just the data collection.)

2.11.4.2 Special Situations (Required)

In conducting interviews on a daily basis with numerous participants, you will encounter special situations. They will be easier to deal with if you have thought about them ahead of time.

The following are some of the special situations you might encounter with WHI participants.

Emotion

- Be prepared for unusual circumstances. Talking about cancer or heart disease can arouse emotion in many people. Participants who have recently lost loved ones, especially to one of these illnesses, may become upset with some questions.
- Remain calm but not distant or cold; let the emotion run its course. Have tissues available. Often participants who have experienced losses express strong motivation to continue with the project to contribute to the disease prevention effort.
- Stop the interview if a participant is clearly unable to finish the visit. Offer a quiet place; get a supervisor or manager to help. If you cannot reschedule immediately, be sure to arrange to call the participant within a few days — just to make sure everything is all right and to try to reschedule the visit.

Strong Objections to Questions

- Assume the burden of communication; take the blame for misunderstandings. If a participant fails to grasp the meaning of a question, admit that perhaps you didn't deliver it clearly and repeat the question. Do not allow the participant to feel that the questions are too difficult for her to answer.
- If the participant is angry, reluctant or impatient about a single question or a series of related questions, cite "the office" or the "researcher." Blame the project for objectionable material, not the participant for being objectionable.
- Respond in a non-defensive tone as though you have heard the objection before. Don't delay the interview any more than necessary; move on to the next question. If the participant pursues the objection, remind the participant that although the researcher had a purpose in including the question in the interview, the participant doesn't have to answer the question.
- If a participant hesitates or refuses to answer, repeat the question. Say, "Let me go over that again. If you don't want to answer, that's your choice; but my instructions are to ask each of the questions." Add that the participant's feelings or opinions about the question are important. If the participant still refuses, accept the refusal graciously and go on to the next question.

Impatience With the Length of the Interview

- If a participant is anxious to finish the interview and says so, say, "I need only a few more minutes of your time. Your answers are important to us, and we'd like to have all of them."

Curiosity About the Research

- Be ready with standard replies for people who want to know more about the research. The *Questions and Answers for CC Staff* in *Section G.1* may help.
- Do not get involved in long explanations of the project, the forms, the research methods, or the outcomes of the study. Be sure to use standard responses.
- Invite participants to talk to your supervisor or Clinic Manager if they wish to carry a discussion further.

Second Guessing Purposes of Questions

- Do not invent your own explanations when participants want you to tell them why certain questions are included in the interview. For participants who persist, tell them that the researcher had a purpose for the question and that you must ask all the questions as they are written.
- Invite participants to talk to your supervisor or Clinic Manager if they wish to carry a discussion further.

Advancing Age

- Gauge your pace according to the needs of the participant. Some older participants may require a slower delivery; others may be insulted by it. (See *Section 20.2.1 - Older Women* for more detailed suggestions on working with older participants in the research setting.)

Hard of Hearing

- For participants who might rely on lip-reading, make sure your face is clearly visible and not obscured by hair, glare, or shadows.
- Slow down for participants with hearing problems and speak in lower-pitched (more bass-pitched, not soft-spoken or high-pitched) tones.
- If you need to increase the volume, move closer to the participant to avoid shouting. Female interviewers often increase their pitch when they speak louder which makes hearing more difficult for many participants who hear lower-pitched tones better. The participant may also turn her "good" ear toward you. Take this cue to speak clearly and distinctly toward that side.

Lack of Understanding or Recall

- Take responsibility for making questions understandable. Do not make participants feel that it's their fault if they don't understand a question.
- Take away the burden of not remembering: participants shouldn't feel ashamed by lack of recall. If a participant doesn't remember a date, lead a discussion back through some prominent seasons or events, repeating the phrase of the question as you go.
- Repeat the question at least once for the participant who does not understand the question. Repeat it twice if the participant has patience for it. After that, record whatever answer the participant offers and go on. Don't risk annoying the participant for the sake of an answer to a single question.
- If a participant asks what a word means, use only the definitions provided on the forms and in the instructions. If there are none, say "Whatever the word means to you." In some instances, you may also emphasize again that the researchers are interested in the participant's feelings and that you "can't really answer for" the participant or "put words in her mouth."

Wandering, Extra Talking

- Focus the participant's attention on the questions, while always being polite. Respond to attempts at idle conversation, no matter how interesting, with brief answers, then return to the form. For example, say, "That's very interesting...now, what would you say about (the question)?" Participants will get the message that you're not going to engage in extraneous conversation (see "Use Body Language" under *Section Section 2.11.4.1-Interview Techniques* above).

2.11.4.3 Guidelines for Suicidal Ideation (Required)

Since distress can vary in severity, so the response by WHI staff must vary. Below you will find suggestions on how to handle three different levels of severity. As state laws governing how to respond to suicidal

individuals may vary, each WHI PI should consult with a mental health professional to determine the best actions to take when severe distress or suicidality is detected.

It is recommended that each site determine those staff who have the level of comfort and sufficient experience to proceed with the assessment described in Level 1 below. Those staff who feel a participant may be seriously distressed but do not feel comfortable with addressing this with the participant, should ask the designated staff who can comfortably proceed to complete the interaction with the participant. The PI at the site should be made aware immediately of any participant with serious emotional distress symptoms, especially suicidal thoughts.

Level l: Significant symptoms of distress (e.g., depression)

Clinic staff who identify significant distress should:

1. Seek further information through paraphrasing to clarify the significance of her distress (I hear you saying . . . Did you say . . . etc). If in doing so the participant does not express suicidal thoughts, proceed with the steps 2-5 below. If she does express suicidal thoughts proceed to Level 2.
2. Recommend to the participant that she consult with her primary care physician who can evaluate and treat her or refer her for specialty care.
3. Request and document in writing (i.e, put in participant's file) permission from participant to follow-up with her within a few days.
4. Notify the responsible WHI clinician or the lead practitioner at the site.
5. Call participant within a couple of days for follow-up.

Level 2: Significant symptoms of distress (e.g., depression) with statement such as "life is not worth living, I wish I were dead."

Clinic staff should refer participant to the responsible WHI clinician (e.g. Clinic Practitioner, PI) for further evaluation. The responsible WHI clinician should assess suicidal intent through direct questioning.

1. If the participant's distress is so bad that she is planning to hurt herself then go to Level 3. If the participant denies that she is planning to hurt or kill herself, proceed through steps 2-6 below.
2. Encourage her to consult her personal physician immediately and offer assistance with that communication (e.g., let her use clinic phone).
3. Request and document in writing her permission to contact a family member. Call family member and inform him/her of the situation. Repeat your recommendation to contact her personal physician as soon as possible.
4. Request and document in writing her permission to contact her personal physician. Call her physician and inform him/her of participant's status.
5. Request permission from participant to follow-up with her within a few days.
6. Call participant within a couple of days for follow-up and notify PI.

Level 3: Significant symptoms of depression with statements indicating suicidal intent

State laws vary regarding the responsibility a staff person has if a participant were suicidal. Therefore, each site should develop a set of guidelines that are consistent with state law. It is recommended that each PI consult with a mental health professional to develop them.

Generally, clinic staff should:

1. Inform the participant of the importance of preventing her from hurting herself. Request and document in writing her permission to contact a family member, friend or family physician. If the participant refuses to tell her family/doctor, inform her that you are obligated to do so.
2. Call family member and/or physician and inform him/her fully. Ask family member to come to clinic site and accompany her to her personal physician's office, local emergency room or community mental health clinic. If no family member is available, accompany her to one of these treatment sites.
3. Develop a policy consistent with state and local laws regarding the CC's responsibility to treat suicide intent. Clinics should consult with a mental health professional (i.e. psychiatrist, psychologist).

2.11.4.4 Guidelines for Domestic Violence (DV)

In the course of interacting with WHI participants, staff will encounter women who disclose or have evidence that they are in a situation involving domestic violence (DV). Since the level of risk may vary, the response by WHI staff can be flexible. State laws may have mandatory requirements governing how to respond to DV. Each CC therefore needs to ascertain any such jurisdictional reporting requirements and apply these within the suggested guidelines that follow. Each CC will also need to identify the staff member, best suited by experience and comfort level, who should interact with the participant regarding DV, and determine how the staff member receiving the original report should respond.

While many staff members may know information about DV, it is frequently difficult to know what words can be used. For this reason specific scripts for assessing the participants status are included within the algorithm below. The purpose is to provide timely, emotionally sensitive support to women who reveal that they are currently or were recently in an unsafe, abusive relationship.

Background

There are many factors that contribute to the difficulty staff have in discussing issues related to DV with study participants. Some of these factors may be:

a. the issue of DV is stigmatized in our society and therefore an uncomfortable subject;
b. staff members may have personal experiences with DV by having witnessed violence in their family or personally being a survivor of DV;
c. the WHI study does not have DV as an outcome, and staff may not have been trained in appropriate assessment and brief intervention for women in situations involving DV.

Always discuss issues of DV in a private setting. Self-disclosure of domestic violence may involve a lot of risk-taking for the woman. This is especially true if the woman has never previously shared this information.

While some women may voluntarily self-disclose currently being in a relationship involving DV, many women will not self-disclose information due to many reasons, including fear of retaliation, low self-esteem, shame/embarrassment, isolation, a perception that the staff is not supportive of issues of DV, and lack of trust in the staff (fear that they will be reported).

Assure confidentiality of her answers.

"Your answers to the questions on these forms are confidential. We will not share this information with anyone," (add "within limits of the law" where there are mandatory state or local laws regarding reporting of DV).

It is suggested that CCs provide resource cards in places accessible to participants such as the women's restroom. These small resource cards can be privately accessed by women and are also an explicit message to participants that the CC considers DV an important women's issue. Posters in exam rooms or restrooms addressing support for abused women may help to communicate to women that your CC and WHI is concerned about DV.

General Preparation for DV

- Compile a list of DV resources for your clinic.
- Perform in-service training for clinic staff.
- Establish liaison with community resources.

Algorithm for Assessment and Resource/Referral Support:

1. WHI participants may disclose that they are in relationships involving DV through their responses to questions on WHI forms (see below) or by mentioning this during a visit.

   Form 37 – Thoughts and Feelings (Ver. 4), Item 97 – "Were you physically abused by being hit, slapped, pushed, shoved, punched or threatened with a weapon by a family member or a close friend?"

   Form 37 – Thoughts and Feelings (Ver. 4), Item 98 – "Were you verbally abused by being made fun of, severely criticized, told you were a stupid or worthless person, or threatened with harm to yourself, your possessions, or your pets, by a family member or close friend?"

   Or

   Form 38 – Daily Life (Ver. 5), Item 52 – "Were you physically abused by being hit, slapped, pushed, shoved, punched or threatened with a weapon by a family member or a close friend?"

   Form 38 – Daily Life (Ver. 5), Item 53 – "Were you verbally abused by being made fun of, severely criticized, told you were a stupid or worthless person, or threatened with harm to yourself, your possessions, or your pets, by a family member or close friend?"

   Participant answers "**Yes**" to any of the above questions.

   Staff response: "I noticed that you answered "yes" to this question about physical (or verbal) abuse and it upsets me. We ask these questions on WHI forms because violence in the home is a significant health risk for women that the study is concerned about. I appreciate your honesty in answering these questions."

   Follow with brief assessment of:

   a. The safety of the woman's current situation. "Was the abuse that you said upsets you something that is happening in your relationship or your home right now?" "Do you feel safe going home tonight, or do you have a friend's house or would you like the name of a shelter that you might go to?"

      If there is current danger and the woman does not want to go to a friend's house or a shelter, ask "Are there guns, weapons, or knives in your house?" If yes, "Where could you take these so you would be safer?"

   b. Her readiness to seek help, "You don't deserve to be in a situation where you are afraid of being hurt. Here is a list of community resources, supportive counselors, and of safe places for you to stay. Do you think that you might be interested in talking to one of these resource people now or in the future?" If the participant does not want the list, then mention, "If at any time you need the phone numbers, we have cards in the ladies room that you can take privately if you wish."

2. WHI participants may present with physical evidence or abuse (e.g., bruises, healing abrasions/lacerations, any type of injury). In these instances, designated staff should establish whether or not these signs are due to DV, and if so should assess the severity of the situation in a similar fashion as described in a and b above, including compliance with state requirements.

   For participants who show no evidence of physical abuse and answer "**No**" to the previously identified questions about DV, resource support cards should be provided in the restrooms.

Resources:

K. Furniss. "Domestic Violence: What Nurses Need to Know."

Kaiser Permanente NW. "Domestic Violence Diagnosis & Assessment."

C.P. Mouton, S. Rovi, K. Furniss, N.L. Lasser. "The Associations between Health Status and Domestic Violence in Older Women: Results of a Pilot Study."

Section 2
Clinical Center Guidelines

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SECTION 3

RECRUITMENT

INTRODUCTION

Recruitment in clinical trials is difficult, usually more so than anticipated. Because study power calculations assume an even flow of randomization throughout the designated recruitment period, careful plans must be devised so that goals can be met in a timely fashion. All the Clinical Centers (CC) made those careful plans. The following is a general list of guidelines to consider to help meet the participant goals for recruitment in the Clinical Trials (CT) and Observational Study (OS).

- Recruitment should start promptly on the targeted date.
- Multiple and varied recruitment strategies are advisable at each site.
- One individual (recruitment coordinator) at each CC site should have overall responsibility for recruitment and be provided sufficient staff.
- Recruitment staffs should have trial-wide networking, including meetings and conference calls.
- Staff turnover should be anticipated, and backup personnel should be trained in advance.
- Staff trained for diverse populations and ethnic matching of staff and screenees can enhance recruitment.
- Recruitment and CC sites should be physically accessible to participants in terms of location, parking, and transportation.
- Clinical Centers should establish accurate systems to monitor their own recruitment progress.
- The medical and lay communities should be well informed about the study before the onset of recruitment.
- Local medical associations and hospital staff members should be contacted by the Principal Investigator at each CC.
- Special-interest groups should receive presentations in appropriate language from the recruitment staff.
- Since the study involves older adults, public relations campaigns should provide a positive image of aging

This section describes **guidelines and recommendations** for recruitment and initial screening of potential participants. Although the procedure for recruitment is more flexible than the procedures for screening, follow-up, and intervention, all plans for recruitment must be described by the CC and submitted to Clinical Coordinating Center (CCC). The process is described below.

3.1. Overview

Recruitment of study participants begins with a plan for the identification of sources of potential participants. The recruitment process begins when the potential participant is invited to express interest in participation, and ends when she comes to the CC for Screening Visit 1 (SV1).

The purpose of recruitment is to:

- Identify groups of potential study participants.
- Introduce the study to potential participants who express preliminary interest.
- Identify potentially eligible women for in-depth eligibility assessment.

The tasks involved in recruitment are:

- Prepare a CC-specific recruitment plan (see *Section 3.2. –Recruitment Plan*).
- Incorporate use of study-wide materials (see *Section 3.3. - Study-Wide Recruitment Efforts*).
- Conduct initial mailings (see *Section 3.4. – Solicitation of Participants)*.
- Conduct screening telephone calls (see *Section 3.5. - Screening Contact*).
- Send the screening packets to eligible women (see *Section 3.6 – Mailing Initial Baseline Forms*).

Clinical Centers are encouraged to identify methods for increasing the efficiency of recruitment and screening. Some CCs will substitute in-person contacts for mailings and telephone calls to enhance their ability to reach certain populations. The data collection requirements remain the same, regardless of the mode of contact. The general guidelines for interviewer-administered questionnaires (*Section 2.11. – Interviewer Procedures*) should be followed when providing assistance to women completing self-administered forms.

Each CC will recruit a portion of the 63,000 CT participants in the Dietary Modification (DM) component and in the Hormone Replacement Therapy (HRT) components over a 3-year period. An additional 100,000 are to be enrolled in the OS component.

3.1.1. Clinical Coordinating Center Role in Recruitment

The CCC is responsible for monitoring, fostering, and encouraging the recruitment effort, and for providing accurate and timely information on the number of participants screened and randomized at each CC. The CCC distributes monthly recruitment activity reports to all participating CCs and the National Institutes of Health (NIH). The reports contain information on all aspects of recruitment, including: yields from each stage of the screening process, actual vs. goal achievements in screening and randomization, etc. These reports serve two purposes: 1) to inspire supportive and constructive collaboration among CCs, and 2) to alert the NIH to study-wide or CC-specific problems early enough to take corrective action.

The CCC Recruitment Coordinator serves as the key contact person for the Recruitment Coordinators at the CCs. The CCC Recruitment Coordinator reviews the CCs' recruitment materials and methods for procedural effectiveness and scientific integrity, passes information and concerns between the scientists and the CC Recruitment Coordinators, keeps the CCs informed of national recruitment efforts, participates in recruitment associated conference calls, provides support in the use of the recruitment database, generates recruitment reports, and trains CC Recruitment Coordinators at central training sessions.

3.1.2. Recruitment Coordinator

Clinical Center Recruitment Coordinators are members of the regional Recruitment and Retention Staff Groups that meet via conference call monthly or as needed during the recruitment period to review progress in recruitment and share experience and expertise. The purpose of these calls is to provide collaboration and

develop camaraderie among recruitment staff. *See Vol. 1 – Study Protocol and Policies, Section 2 – Protocol, Section 10 – Study Organizations*.

3.1.3. Recruitment Activities Data Collection (Required)

To capture information on the efforts of the CCs to identify women who might be potentially eligible and interested in participating in the study, the CCC provides *Form 1 - Recruitment Activity Summary*. This form is intended to collect data on the number of mailings, advertisements, news articles, public service announcements, presentations, etc., that a CC does during a 1-month period. The CCs complete and submit the form to the CCC on the first working day of the month for the previous 1-month period. One of the requirements of the form is that the CC attach any recruitment materials developed during the reporting period (for example, press releases, public service announcements, newspaper articles and advertisements, posters, cards and other marketing tools). The CCC keeps these materials in a library of study-wide and CC-specific recruitment materials.

3.1.4. System for Addressing Problems in Recruitment

It is essential that recruitment for the study be completed in a timely manner. Monthly recruitment reports distributed by the CCC are reviewed and addressed by PIs, staff groups, subcommittees, CCC, or the NIH Project Office. See *Vol. 1 – Study Protocol and Policies, Section 2 – Protocol, Section 10 – Study Organization*. Questions about protocol and procedures may be directed to the CCC via the Inquiry Reporting System (IRS). (See *Section 1.4.2 – Methods of Communication* and *Form 171 – Inquiry Form*.)

3.1.5. Guidelines for Developing Recruitment Materials

The following guidelines should be considered when preparing all recruitment material. They include suggestions about content, visual design, writing style, printing and mailing. These guidelines will be used by the CCC when reviewing recruitment materials developed by individual CCs.

Content

- Be brief. Include only what the reader needs to decide to contact you. Ask yourself, "Would I really read this after a busy day?"
- Put the most important points first and last. Use a logical sequence for the rest.
- Keep language appropriate at about a 6th grade level.
- Do not make false claims or promises (for example, do not include: "By participating in the study you will lose weight, live longer," etc.).
- On brochures or letters with an enclosure card or tear off, consider the need for confidentiality. Do not ask for personal information.
- Do not discriminate. The contents of materials you send to a particular group should be the same as that given to other groups, although the style may differ.
- Pilot test developed materials. Show the materials to age-eligible women not connected with research for only a few seconds, then ask, "What would you say this is all about, in your own words?" Then ask them to read it over more slowly and tell you what it is about. Revise materials if necessary and then retest.
- Include: "funded by the National Institutes of Health."

Visual Design

- Make sure that the visuals draw the eye to the two or three key points.
- Consider inclusion of your own institutional seal for credibility.

- Include the study logo and catch phrase on all recruitment pieces, including posters.
- Include lots of white space in the margins and between blocks of text.
- Use illustrations (simple line drawings are best) to reinforce information and direct the eye to the key points.
- Show the material for a few seconds to some age-eligible women not connected with research and ask them what they notice first, what they remember, what they should do, etc.

Writing Style

- Use a simple and relaxed conversational style. Don't be afraid to use the word "you." Ask yourself, "Would I talk like this to my grandmother?"
- Avoid large blocks of text. Break information into bulleted lists whenever possible. Ask yourself, "Can I scan this in a few seconds and find what I need?"
- Use the active voice. State subject and verb directly instead of describing object as acted upon by an unstated subject. For example, use "You will receive these benefits" rather than "Benefits provided include." Be direct and personal.
- Use short and simple words (for example, "assigned by chance" rather than "randomized"; "handouts about" rather than "handouts pertaining to").
- Use short and simple sentences with as few qualifying phrases as possible. The best structure is: subject, verb, object. Limit each sentence to one idea.

Printing

- Prepare camera-ready (not Xerox) copies for the printer.
- Print on at least a 60-pound paper if double sided. Self-mailers are often printed on 65-pound paper.
- Letters must be on your institutional, a referring agency's institutional, or WHI letterhead with an official signature and timely date.
- Color of type print and paper should be consistent with and complement those agreed upon for the study. Black print on white or yellow is the easiest to read.
- Type style and size for the text should be consistent and should be 12 point or larger. Do not use script or sans serif fonts. These fonts don't have the squiggles on the ends of the lines and therefore make letter recognition harder.
- Do not use all capital letters, even in titles or headings. Capital letters are more difficult to read and recall. Use larger and bolder print instead.

Mailing

- Type or handwrite addresses on mailing envelopes. Participants may respond positively to handwritten envelopes but time and cost factors may prohibit this strategy. Postal regulations state that one may handwrite the name and address when using bulk mailing, but anything else handwritten on the envelope is considered a message and is prohibited.
- Do not knowingly mail to the same individual more than three times.

3.1.6. Participant Material Review Recommendations and Guidelines

Participant materials are written materials given to women at any time during screening or participation in WHI. CCs should submit participant materials to their local CC's IRB and the CCC for review and approval. When submitting materials to the CCC, please indicate when and how the materials are to be used. Materials such as print adds or PSAs are not considered participant materials and do not need to be reviewed.

During CCC review of participant material, we have identified some common themes in these materials that are summarized here. Basic recommendations for preparing participant materials are contained in *WHI Manual Volume 2, Procedures, Section 3.1.5. – Guidelines for Developing Recruitment Materials*.

Nutrition Materials:

Articles, handouts, newsletters, and posters containing information on nutrition are not allowed for distribution to potential participants. This information can influence and/or contaminate women who may join the Dietary Modification part of the study. Although it is understood that nutritional information is widely available to the general public, the study cannot be directly responsible for distributing such materials.

HRT/Clinical Materials:

News or scientific material concerning menopause and/or hormone replacement therapy (HRT) should not center on its benefits or risks, but rather on the need for further research to answer the questions raised by HRT usage. Articles which promote HRT or alarm women may serve to discourage them from volunteering or continuing their participation in the WHI. This is because they can develop feelings of either needing to take "real" hormones (not potentially be randomized to a placebo), or making sure that they avoid hormones.

Terms:

Some terms and facts have been revised and/or corrected, based on recent committee decisions or procedural clarifications. Some of the revisions/corrections to keep in mind are listed below.

Commonly Used Terminology of Fact:	**Correct Terminology of Fact:**
avoid exercise for 8 hours before	avoid exercise for 12 hours before
Dietary Change Program	Dietary Program
Dietary Intervention Group	Dietary Change Group
Food Frequency Questionnaire	Food Questionnaire
low-fat diet	low fat, high fruit, vegetable, and grain dietary pattern
practice pills	study pills
run-in period	enrollment period
study hormone medications	study pills
the largest study ever on women's health	one of the largest studied ever on women's
Usual Diet Group or Dietary Control	Dietary Comparison Group

Phrases:

To avoid giving an incorrect impression of the study or of a woman's participation in the study, some conditional phrases are recommended.

Unconditional phrase:	**Conditional phrase:**
study is looking at how to improve	study is looking at ways to improve
will answer questions about	may help answer questions about
will improve your health	may improve your health
you will receive	you may receive

Readability:

The reading level of participant materials is very important. It may not be widely known that to follow the instructions on an aspirin label requires a 10th grade reading level while one if four American adults reads at a 5th grade level or below. Also, the grade level achieved in school is not a measure of an individual's reading skills. You can use Microsoft *Word*™ to evaluate a document using he Tools menu and selecting Grammar. Several suggestions for improving a document's readability are listed below.

- **Use the active voice where ever possible:** State the subject and verb directly instead of describing an object as acted on by an unstated subject. Speak directly to the participant. The passive voice often makes your writing less clear because it often leaves out who will do the action.

  Active voice: We will give you the test results.

  At this visit, we will tell you more about the study.

  Please do not eat for 12 hours.

  Passive voice: Test results will be given to you.

  At the visit, women are told more about the study.

  Women are asked not to eat for 12 hours.

- **Use shorter sentences and words:** Participant material is made more readable by using shorter sentences and simpler words, less wordy phrases and more positive wording. Many people have a hard time following the key point in a long sentence, particularly if it has a lot of clauses. Ideally, sentence length will vary so the reader won't find the material monotonous. An average readable sentence length in American English is 17-23 words. If your sentence is over 25 words, your writing may be difficult to read. A long word has three or more syllables.

  Shorter sentence: Studies will help decide how best to prevent these diseases. (10 words)

  Longer sentence: As a result, recommendations for successful prevention and treatment of these diseases cannot be made with confidence, due to the lack of adequate clinical testing. (25 words)

  Shorter word: about

  Longer word: approximately

- **Use simple phrases:** Use a simple and relaxed conversational style.

  Simple phrase: Women can be part of the answer.

  Wordy phrase: Women now have the opportunity to be part of the answer.

- **Use positive wording:**

  Positive wording: Please do not exercise.

  Negative wording: You will not be able to exercise.

- **Minimize medical jargon and avoid technical terms:** When medical jargon is necessary, define the medical term immediately after it appears in the sentence.

- **Words:** Some words commonly used in WHI are not familiar to the lay public or have negative connotations. Therefore we suggest using simpler substitute words when preparing participant materials. A list of recommended words is given below.

Commonly Used Words:	**Recommended Substitute Words:**
approximately	about
assistance	help
cardiovascular disease	heart disease
clarify	make clear
compensate/reimburse	pay
concerning	about
conclusion	end
consult the map	use the map
currently	now
diseased afflicting women	diseases in women
dispense	give
do not hesitate to call	fell free, please call
e.g.	for example
eligible	if you can join
endometrial aspiration	test of the lining of the uterus or womb
experiment	study
exposed/exposure	worked with/lived with
i.e.	that is
immediate	right away
impact	make a difference, effect
in order to	to
in the absence of	without
intervention/treatment group	women in the Dietary Change group/getting active pills
medication	study pills or pill bottles

Commonly Used Words:	Recommended Substitute Words:
myself	me
notify you	let you know
osteoporosis	osteoporosis (weak or brittle bones)
participate in	join or take part in
pelvic exam	female or internal exam
placebo	inactive pills
postmenopausal	change of life
prior to	before
procedures	tests, exams, activities
provided	given
randomized	group is chosen by chance
remain	live or stay
require	ask, need
research	study (some ethnic groups think of experiment or exploitation when they hear the word research)
reside	live
select	choose
similar	like
study arm/component	study part/programs
subjects	participants, women
submitted	given
trial	study
uterus	womb
voicemail	a recording machine

Formatting:

- **Use 12-point Serif fonts:** Participant material is more readable if a ≥ 12-point font is used (the font used here is 12 points). The ideal font size for older populations is 13 or 14. Do not use *script*, or sans serif fonts. Sans-serif fonts don't have the squiggles (serif) on the ends of the lines that make the letter recognition easier. Serif type is the most familiar style (this type is Times New Roman) and the easiest to read. Mixing several types styles on the same page may also be confusing.
- **Use upper and lower case:** Use upper and lower case letters even in titles and headings. CAPITAL LETTERS are more difficult to read and recall. Use larger or **bolder** print or underlining instead.
- **Preserve white space:** Do not crowd too much information on a page. During screening, you have three screening visits and several months to convey the complex information regarding the Women's Health Initiative to the potential participant.

3.2. Recruitment Plan (Required)

Each CC prepares a detailed recruitment plan following guidelines provided by CCC. This includes a complete calendar of all events related to recruitment activities with specific attention to the initiation of recruitment strategies and their subsequent regular, periodic evaluation. Mass mailing drop-dates, media coverage, and community events that the CC is participating in or presentation to lay and professional groups, etc. are noted on the calendar. The calendar can be used to evaluate the effectiveness of past strategies and to plan future ones. In the case of media coverage or publicity the CC can plan for an increase in public response.

Peer review of each CC's plan will be carried out by other RCs at training workshops. The CCC will retain a copy of all recruitment plans. Subsequent updates will be submitted to the CCC at six month intervals.

Each of the CC plans should contain the following information:

- A description of the primary and backup catchment areas (in grant application).
- Census or other data on the target population (women between 50 and 79 years old).
- A description of specific recruitment approaches that will be used and in what order.
- Estimates of yields from the specific approaches based on past experience.

Each plan should describe backup strategies that can be quickly employed if the primary strategies result in a less than expected yield. A minimum of three months and up to six months may pass before the results of a newly implemented strategy is evident. Most CCs use an integrated approach to recruitment, employing most, if not all of the following approaches discussed below simultaneously.

3.2.1. Targeted Mass Mailings

All CCs are encouraged to employ a major direct mail campaign, involving tens of thousands of mailings to women in the target age group. Age-eligible women can be identified through a variety of sources: motor vehicle registration lists; drivers' license lists; Health Maintenance Organization (HMO) membership databases; voter registration tapes; Medicare enrollee lists; health insurers' lists; commercial mailing list brokers, etc. These sources usually include name, address, age, and gender. In addition to these general sources of age-eligible women, many CCs have identified several other enriched sources of participants. These include databases containing some clinical information as well as general demographics, such as breast cancer screening clinic patients or screenees or participants in previous clinical trials. The above described mailing lists are invaluable resources.

Previous experience suggests that second and even third mailings using the same list can increase the yield slightly. Because most mailings from the CCs use bulk rate (third class) it may take at least a week for the Postal Service to deliver, and another week for the reply card to be returned. Therefore repeat mailings should be spaced at least three or four weeks apart.

Another approach is to repeat mailings according to response. If the response is low from a specific age-group or zip code, remail at a different time of year. For the older age group, choose good weather and moderate temperatures. Exclude the holiday seasons from mailings. If the response is good to the first mailing, remail at the same time of year on a yearly basis. Those not able to consider participating when you first mail may be available the next year. If the remailing is done from the CC rather than an HMO or other organization, a cover letter should mention that you have sent them information previously. Also, mention of recruitment statistics may spur some women to respond. For example, “In the past year, 500 women have enrolled in the Women’s Health Initiative…”.

To facilitate formation of intervention groups for the DM component, it may be preferable to target mailings within geographic areas or zip codes.

Mailings usually consist of a letter inviting women who are age eligible to return a form or postcard indicating their potential interest. Include a brochure describing the study (see *Section 3.3.3. – WHI Recruitment Brochure*) with a postage-paid return envelope or postcard. An interested woman can either call or mail in her response.

3.2.1.1. Identification of Sources of Names

Each CC identifies potential participants through various referral sources. The nature of these sources depends on the target population of the CC. The procedure for identifying potential participants varies by referral source and CC.

In each case, negotiations are made with the individual sources. Some sources provide mailing labels, while others require the CC to furnish recruiting materials for mailing by the source.

It is best to target groups with whom you already have a relationship and to maintain visibility with them. It is important to establish ongoing relationships with the agencies that have agreed to cooperate.

Do not assume that the negotiations will be completed quickly. Experience suggests that some negotiations may take months to finalize. Thus you will need to develop these relationships many months in advance of planned initial mailings to avoid delays in the recruitment schedule.

Monitor the success of various recruitment strategies and referral sources. This information is used to streamline the process and troubleshoot recruiting problems for all CCs. To monitor recruitment, assign a 3-digit number to each different referral source and different recruitment strategy you use. For example, brochures handed out at health fairs, presentations, or to individuals to pass out to their friends and co-workers would be three different referral source codes. Assign two referral source codes to a source to which you do two mailings, one for the first mailings and a different number for the second mailings. For example, a CC doing second mailings would assign the following referral source numbers:

101 Organization A - first mailing

102 Organization A - second mailing

201 Organization B - first mailing

202 Organization B - second mailing

Monitoring the return and eligibility rates of these sources can guide you in future recruitment plans. Clinical Centers can monitor this in several ways: add a referral source code (RSC) in the recruitment database (RDB) available through the CC; use a user-defined field in the WHILMA database, or on *Form 2/3 – Eligibility Screen*.

3.2.1.2. Using Sources for Preliminary Screening

The screening of potential participants begins with the initial identification of individuals. Because of the time and cost spent in screening potential study participants, the referral sources should know and publicize only <u>limited</u> eligibility criteria.

Give out only the following eligibility criteria to individuals not associated with this study.

- The participant must be aged 50–79.
- The participant must be female.
- The participant must be postmenopausal.
- The participant must be able to attend regular CC visits.

The ability to assist with this limited eligibility review varies from source to source, depending on its available information. Usually, screening at the source level is limited to screening lists for age-eligible women. It is best to begin with sources that have the largest numbers of potentially eligible individuals.

3.2.2. Priming the Community

All CCs should identify techniques to be employed before embarking on recruitment, including informing the medical community, the community-at-large, and the special communities providing services to older adults, special populations and/or women. Clinical Centers can mail letters to physicians and medical societies in the local area describing the study, requesting referrals and giving assurances that the goals of the study do not conflict with or supplant the primary care physician (*see Figure E.1.1. – Model Letter to Community Health Care Providers and Physicians*). The lay community can be informed through general press releases (see *Figure E.1.3. – Model National Press Release*) in the local print and visual media or radio and TV talk shows featuring interviews with study investigators, public service announcements (PSAs) on TV or radio, and feature articles in specialty magazines, newspapers, newsletters, etc., targeting older women. Good rapport with the community is essential to successful recruitment.

3.2.3. Mass Media

Recruitment can be planned and promoted through various marketing and publicity strategies. These methods vary between CCs.

The CCC can provide the CCs and their institutional public relations personnel with sample press releases or CCs can prepare their own (see *Section 3.1.5. – Guidelines for Developing Recruitment Materials*).. The material released should be fairly specific for the population of interest. Send a copy of all publicity materials to the CCC Recruitment Coordinator for inclusion in the recruitment materials library. The CCC RC will review these materials using the same guidelines.

Clinical Centers must be prepared to handle, by letter or telephone, the response from the public immediately after the media publicity goes out, including national publicity (for example, NIH announcement of new CCs). A contact phone number is essential. If an answering machine is used, let participants know so they won't expect an immediate response and can feel comfortable leaving a message. Press releases should not be sent out until the CC is organized to handle the response. Responses to media messages will vary. Plan to do press releases based on human interest and pubic events (for example, the opening of CCs, Mother's Day, etc.). Be certain the press release contains some new information. Don't be too optimistic that the responses will continue for long. It is surprising how quickly the calls stop after a newspaper article or PSA has run. Plan to do another release in a few weeks.

All CCs should plan to use the media, such as local television news spots, newspaper feature articles, etc., for informing the community and for requesting volunteers for the study. For CCs that are especially successful using mass media as a recruitment tool, this may be the source of most of their participants. For most, it will more likely be an adjunct to a primary strategy of mass mailings. The media messages should communicate that the volunteers must be generally healthy women aged 50–79. The effective coordinated use of mass media along with mass mailings can result in dramatic increases in response.

CCs using sequential geographic recruitment strategies to facilitate DM group formation may not want to use mass media as a primary recruitment tool or may need to modify their responses to call-ins generated from publicity.

3.2.4. Community Activities

Clinical Centers can participate at health fairs, blood pressure screenings, or other women's events such as "Race for the Cure," to pass out brochures and be seen by the community. You can identify the organizations, agencies, and group residences that have older women as their clientele and make arrangements to address these groups and solicit participation.

3.2.5. Medical Records

Some CCs will screen medical records as a backup strategy. From medical records it is possible to identify potential participants who meet basic eligibility requirements. Once potential participants are identified in this way, it is most effective to have the invitation for screening come from the personal physician. For example, a CC might plan to give brochures and invitations to all age-eligible women attending a large radiology group practice. Specific medical record review is very labor intensive.

3.3. Study-Wide Recruitment Efforts

Although the individual CCs bear the responsibility of recruiting participants for their CC, study-wide efforts using the same or slightly modified recruitment and orientation materials at each CC can enhance visibility and bonding with the national study. For example, when all CCs begin recruiting, there will be a national public awareness and recruitment campaign using appropriate materials, national television shows, magazines and public service announcements (PSAs) with prominent spokespersons. The CCC will coordinate this campaign with a public relations firm and input from the Recruitment and Retention Staff groups, WHI committee structure, and the NIH Project Office.

3.3.1. Video Tapes

The WHI will produce at least four videos. One video will provide a brief (10-15 minutes) overview of the study to be used either for recruitment, at the time of screening, or during a group orientation meeting or community presentation. One video will be used for initial consent. Two videos discuss the risks and benefits of being in the CT and will be used as part of the informed consent process for DM and HRT.

3.3.2. WHI Logo and Catch Phrase

The study is so long that family and community support will be invaluable in the long run to keep women in the study and participating fully. Community recognition and support will also encourage women to participate until the end of the study. To generate this family and community support there must be wide recognition of the study and respect for those who are participating.

The WHI logo was designed as a visual strategy to generate recognition of the Women's Health Initiative among the general public and women in particular. It emphasizes that the study group is women. The catch phrase "Be part of he answer" emphasizes that women have a chance to participate in the study of women's health. See *Figure 3.1. – WHI Logo and Catch Phrase*. You can obtain an electronic copy of the logo from the CCC. The logo is an elegant, stylized depiction of mature women. The study colors are attractive and eye catching; blue (Pantone 287) and purple (Pantone 252). The colors are used effectively in a bleeding pattern on the study-wide brochure and medicine bags.

- Posters sporting the WHI logo and catch phrase can be used at health fairs and presentations, worksites and clinics, clubs, markets, libraries, and pharmacies to name only a few possibilities.
- Study materials should display the logo and can use the catch phrase on stationery, brochures, CC interest questionnaires, appointment reminder cards, birthday cards, note cards and invitations to participate.
- Recruitment and retention incentive gifts should display the logo and catch phrase on items such as pins, pot holders, memo pads, photo pins, or tote bags.

3.3.3. WHI Recruitment Brochure

A study-wide brochure has been developed for the WHI to be used by all CCs in their mailings or presentations. CCs can mail the brochure separately or include it in a mailing with a cover letter and interest survey. Brochures are printed with the same information for all CCs but with CC-specific information on one panel and on a tear-off, postage-paid return postcard. The brochure asks and answers general questions about the study and lists the CC's address and phone number. On the postcard, the woman is asked to provide her full name, current address, home and work phone numbers and to check how she heard about the study. The CC can write a referral source code on the postcard to aid in identifying the source to which the woman responded. The brochures are printed by the Government Printing Office (GPO). Clinical Centers order them quarterly through the CCC. See *Figure 3.2. – WHI Recruitment Brochure*.

If CCs choose to develop their own promotional brochure, it should conform to the criterion in *Section 3.1.5. – Guidelines for Developing Recruitment Materials*.

3.3.4. Slide Presentation

The Publications and Presentations Subcommittee of WHI has developed slides for professional presentations that are produced and distributed to all CCs. They should be reviewed and updated periodically. The slides vary in degree of complexity and detail. Individual CCs can therefore tailor the slide set used for presentations to physician groups, grand rounds, or other professional groups These slides may have limited usefulness for older laywomen. Additional slides are being created for lay presentations. Paper versions of these slides will also be provided if CCs want to make overhead transparencies.

3.3.5. Press Releases

Figure E.1.3. – Model National Press Release shows a sample press release that can be used as a model. See *Section 3.2.3. – Mass Media*, paragraph 3 regarding use of and response to press releases.

3.3.6. Public Service Announcements (PSAs)

PSAs should address the importance of WHI because many health concerns of women have been neglected by researchers in the past. Include that there is now an opportunity for women to "be part of the answer" in women's health. Present the choice to take action for the benefit of future generations of women. The benefit to an individual woman's health through screening and monitoring at no cost can be stated. Some PSAs could address ethnic barriers to health care and research studies. The special needs of diversity in literacy levels, ethnic backgrounds and culture also need to be taken into account.

Two examples of 30-second PSAs are:

> "Heart disease, cancer, and thinning bones are diseases that kill or disable a growing number of women each year. You can be a vital part of a nationwide study to determine ways to prevent these illnesses. Help launch a new era in women's health by participating in the Women's Health Initiative. If you are 50 to 79 years of age, you can make a difference, not only for women's health today, but that of future generations as well. Start your journey to a long life with a healthy heart and spirit. To register, call your toll-free line at…"

> "Heart disease is the number one killer of women in the United States. Breast cancer will affect one in every nine women. Weakening bones disable nearly 30% of women over age 75. You can help change these staggering statistics by joining one of the largest health studies ever conducted. (Local CC) is leading the way in the Women's Health Initiative – a nationwide study of factors that affect women's health. If you are 50 to 79 years of age and want to lay the foundation for women's health today and that of future generations, call our toll-free line at…"

3.3.7. Spokespersons

National and local spokespersons to spearhead PSAs on radio and TV could reach different populations through different media. Spokespersons of diverse ethnic backgrounds and ages are essential to appeal to different women. It will be critical to have spokeswomen who are recognizable to a broad range of American women. Possible candidates may be drawn from the following sectors:

- Celebrities
- Politicians
- Writers and journalists
- WHI PAC (Women's Health Initiative Program Advisory Committee)

3.3.8. Television

Television can be used most effectively to make the WHI well known to women and the public in general. WHI can be featured on local women's health programs. Talk shows might feature WHI when discussing women's health issues. Talk shows on Spanish networks can be especially effective for recruitment of Hispanic women. The under representation of minority women in many important research studies could be one topic that illustrates the special nature of the WHI.

3.3.9. Print Media

Magazines and Newsletters

- A number of national magazines identified to target for WHI articles are: TV Guide, Family Circle, Readers Digest, Redbook, Woman's Day, Ladies Home Journal, Working Women, American Health, People, Newsweek, Time, Vanity Fair, Ms., AARP Newsletter, HMO magazines and newsletters, employee trade magazines, etc.
- Press releases, could be sent to identified publications and writers.
- Clinical Centers should alert the CCC to any proposed national coverage so that all CCs can be alerted and prepare for the publicity.

Newsprint

- Prepare press releases and/or press conferences throughout the year and for Mother's Day, emphasizing that participation in WHI is a lifelong gift from mothers to their daughters' and granddaughters' future health.
- Identify newspapers with wide circulation in your area.
- Identify interest angles specific to each newspaper. Human interest articles featuring disease detection during screening or mother/daughter participants, for example, would stimulate interest. The angles should be attention getting and readership appropriate.
- Prepare news releases targeting various interest areas, for example, lack of women in research, lack of minorities in research, human interest, etc.
- Write a letter to health editors (or science, food, or lifestyle editors) with a news release. Follow up with a call to the health editor within one week.

Columnists

- Freelance writers and syndicates columnists who write regularly for local newspapers or magazines should be identified and contacted to encourage them to explore WHI issues as potentials subject matter.
- Get samples of columns from each paper to model news releases.
- Develop an angle(s).
- Write a letter to each columnist. Follow up with a call within one week.
- Establish a mechanism to tabulate and distribute on a monthly basis all written national promotion pieces.

3.3.10. Recruitment Video

Plans are underway to produce a WHI recruitment video as an upbeat marketing tool for use at community presentations and initial screening visits.

Some important themes are:

- Reasons for importance of WHI.
- Lack of research data on women.
- Benefits of participation.
- Components of the clinical trial.
- Women of different ethnic backgrounds and economic status in the video.

3.3.11. Timeline

Clinical Centers should develop and finalize a timeline of specific recruitment efforts 8-12 weeks before projected implementation dates for events such as those listed below.

- Holidays like Mother's Day (May)
- Special women's events such as National Breast Cancer Awareness Month (October), American Heart Month (February), or The Susan G. Komen Breast Cancer Foundation's Race for the Cure (all months of the year in different cities)
- Spring and fall, which are optimal recruitment months

For example, development should begin in February for April/May activities and in July for September/October activities.

3.4. Solicitation of Participants

Potential participants may be solicited using various strategies. One strategy is mass mailings using voter registration lists, Department of Motor Vehicles (DMV) lists, Health Care Finance Administration (HCFA, Medicare) lists, HMO lists, etc. Another strategy is participation in community activities like health fairs, civic celebrations, clinic openings, open houses, etc. Another valuable strategy is to employ local media in the form of PSAs for television and radio, participation in health programming, principal invegtigator interview, news stories and paid advertisements. All of these strategies may be used simultaneously in order to reach a wide and varied population.

3.4.1. Mass Mailings

The initial contact with a potential participant is usually a mailing that includes an introductory letter and the recruitment brochure with a return postcard, interest survey or prescreen. Send a draft of the introductory letter to the CCC for review and placement in the study-wide and CC-specific recruitment materials library. Follow *Section 3.1.5. – Guidelines for Developing Recruitment Materials*.

- Initial contact letter (see *Figure E.2.1. – Model Initial Contact Letter*): typically a 1-page letter that includes:

  a) A statement of introduction from the referring agency, if applicable.

  b) A statement that participation in the study is completely voluntary and does not affect the individual's relationship with the referring agency.

  c) A brief description of the study.

  d) An explanation of the enclosed prescreen or interest survey, if included.

  e) A statement requesting the individual to complete and return the interest survey, prescreen or postcard or call the CC.

  f) A statement thanking the individual for completing and returning the prescreen or postcard and stating that eligible participants will be contacted by the CC.

The letter is usually printed on the referring agency's or WHI stationery and mailed in a corresponding agency envelope. Some CCs may mail directly.

- Recruitment Brochure

  See *Section 3.3.3. – WHI Recruitment Brochure* and *Figure 3.2. – WHI Recruitment Brochure*.

- Prescreen

  Clinical Centers may choose to include a brief prescreen (see *Figure E.2.3. – Model Prescreen*) with the letter rather than a brochure with return postcard. If a brochure is also included, remove the return postcard to avoid the women responding twice. The CC is responsible for preparing its own prescreen with the recruitment source identified on the prescreen. The prescreen can include questions about the woman’s age, availability for CC visits over the next three years, and other broad eligibility questions (for example, current hormone use, cancer history, heart attack or stroke in the past six months, menopausal status). Initial eligibility and interest can be assessed quickly using a prescreen.

- Interest Survey

  An interest survey (see *Figure E.2.2. – Model Interest Survey*) may be included with the initial contact letter in addition to a brochure. In this case, a return postage-paid envelope is also included. The interest survey is a first step to determine if the woman is interested in participating and whether further contact should be made. It establishes the best time to follow-up with phone contact and is a preliminary screen for age and gender.

- Return Envelope

  The return envelope is a postage-paid business reply envelope addressed to the CC for returning the prescreen or interest survey. The return envelope is not necessary if the brochure with return postcard is used.

3.4.1.1. Preparation of Initial Contact Mailing

Mailings can be prepared in several ways. Small mailings (1–2,000) can be prepared at the CC. Large mailings (2,000 or more) can be prepared efficiently and economically at the CC only if the referring agency provides the names on diskettes or if the CC has access to other needed facilities, such as computer equipment and tape drives. If these facilities are not available, CCs can use local printing agencies to assist in preparing mass mailings.

3.4.1.2. Duplicates

Women may receive initial contact letters from more than one source agency. This can occur when the individual is on the mailing list of several referral agencies. For example, an individual may be recruited from a breast cancer screening clinic as well as a list of Medicare enrollees. Removal of duplicate names is often not possible because: 1) confidentiality requirements of some agencies do not allow the CC to have access to the names of individuals on the mailing lists; and 2) time and costs for removing duplicate names on accessible lists are prohibitive. In addition, experience has shown that individuals may respond negatively to letters from one agency but be willing to participate when contacted by a different agency or after learning that friends have participated.

3.4.1.3. Responses

Clinical Centers must anticipate that not all the addresses used for the mailings are correct or current. The percentage of out-of-date or incorrect addresses varies depending on the referring agency and date the addresses were prepared. Clinical Centers should advise the referring agencies that returns can be expected. They man be willing to attempt to contact these individuals.

3.4.1.4. Anticipated Return Rate

The anticipated rate of return varies by referring agency. Pilot studies for WHI suggest that between 5% and 30% of women will respond to the initial mailing. A proportion of these responses may be refusals. It is important to keep track of the rate of return by referring agency. (See *Section 3.2.1.1. – Identification of Source of Names*.)

If an individual calls the CC rather than returning the postcard or prescreen, CCs may complete the prescreen over the phone or conduct the screening contact on *Form 3 – Eligibility Phone Screen*.

3.4.1.5. Processing Responses

- Stamp the date on each response as it is received.
- Review the name and address on the postcard, interest survey or prescreen for completeness and readability. Occasionally, the name and address may be incomplete or unclear on the interest survey or prescreen while it is legible on the return envelope. In such cases, transcribe the information from the envelope to the interest survey or prescreen before discarding the envelope.
- If applicable, review the prescreens for potential eligibility and any comments regarding participation. The goal at this point is to eliminate from further screening any individuals who are clearly uninterested or ineligible. All other respondents should be considered potentially eligible.
- Sort the prescreens into the following three categories:

- Ineligible due to age or other information provided. Indicate on the form that the participant is ineligible. File all ineligible responses for future reference.
- Possibly eligible for the CT; screening phone call required.

  Add the woman's name to the list of women to be called, including best time of day to call. Proceed to preparation for Screening Contact. See *Section 3.5. - Screening Contact.*
- Possibly eligible at future date. This includes individuals who:

  a. Are too young now, but will be age-eligible before your recruitment phase ends.

  b. Are not immediately available to come to CC visits, but will be during the recruitment period.

Indicate on the form when the individual may be eligible in the future. File the form by date of possible eligibility with other prescreens of individuals who are possibly eligible at a future date. Review this file on a monthly basis and proceed to the screening contact preparations for those individuals who reach the recorded date.

3.4.2. Mass Media

Recruitment through mass media will be used by many CCs, either alone or in conjunction with mailing strategies. Depending on the emphasis, CCs need to adapt the steps and allocation of resources in the recruitment process to handle the uneven load.

The simplest approach to incorporating mass media campaigns into recruitment is to consider each media release and its subsequent response as an additional source of names. Responses to each campaign can then be monitored and evaluated for efficiency and success in reaching target populations.

For call-in responses, the CC may choose to have a recording describe general aspects of the study and request that the caller leave her name and phone number if she is still interested. An interviewer would then call the woman back and proceed with the screening interview. See *Section 3.5. - Screening Contact*. Alternatively, if CCs have staff available, a trained interviewer can take the call and complete the screening interview.

3.4.3. Community Activities

Clinical Centers that choose to use community activities such as presentations to particular groups, hosting booths at health fairs, etc., also need to plan well ahead for varying levels of activities. The different forums require the CC to determine to what extent recruitment and prescreening can be completed in a single encounter. In some circumstances it may only be feasible to provide the WHI Recruitment Brochure and an opportunity for the woman to express her interest. In other settings it may be reasonable to complete the screening interview (*Form 2/3 – Eligibility Screen*) and *Form 60 – Food Frequency Questionnaire (FFQ)* and determine initial eligibility for HRT and DM. This contact is referred to as Screening Visit Zero or SV0. It is the responsibility of the CC to determine the feasibility of completing the recruitment and prescreening activities in the various settings. The documentation of these efforts can be managed using the same system for identifying sources of names and number of responses.

3.5. Screening Contact (Required)

The WHI requires the collection of screening data using either an interview-administered (*Form 3 - Eligibility Phone Screen)* or a self-administered format (*Form 2 - Eligibility Screen*). These forms contain the same data items but the format is changed to make it suitable for the two methods of data collection. Clinical Centers may use a prescreen (as described in *Section 3.4.1. – Mass Mailings*) but must complete *Form 2/3 – Eligibility Screen* to continue screening the participant further.

A screening contact is completed on all women who return a prescreen, postcard, interest survey, or otherwise express interest and who initially meet the study eligibility criteria. Women may be recruited in such ways that this contact is done in person or by mail. Clinical Centers choosing to have the form completed by the participant will use *Form 2 – Eligibility Screen*. For example, Some women may be recruited through community organizations. Such women may be initially screened at an organization meeting. If women do not have telephones and are randomized/enrolled, careful planning must be done to ensure adequate follow-up. The self-administered versions of the screening questionnaire (*Form 2 – Eligibility Screen*) can be used for these settings. All interview-administered eligibility screens will be completed using *Form 3 – Eligibility Phone Screen*.

This section focuses on the screening telephone interview (*Form 3 – Eligibility Phone Screen*). The estimated time to complete the screening phone call is 15 minutes.

3.5.1. Purpose

The purpose of the screening contact is to:

- Explain the purpose and the requirements of the CT to those participants who responded to the initial contact letter by returning the prescreen, interest survey or postcard, or who called the CC to express interest.
- Ask the woman specific questions related to the eligibility criteria for CT participation in general and HRT and DM specifically.
- Schedule an appointment for SV0 or SV1.

3.5.2. Phone Procedures

Usually, CCs should complete the screening contact within three weeks of the return of the prescreen, interest survey, postcard, or phone contact to the CC. Attach a *Form 3 – Eligibility Phone Screen* to each prescreen, interest survey, postcard, or phone response you have sorted into the category "Possibly Eligible."

Prepare to do several phone calls in any one session. You may find that using a telephone headset is less tiring than using a standard telephone handset when doing many calls. Frequently, you will not be able to complete all the contacts you set out to do. The individual may not be home or the phone may be busy. A grid for recording the date and time of all phone attempts is on *Form 3 - Eligibility Phone Screen*. If you are unable to complete a phone call at a particular time and day, try calling at other times and days.

3.5.2.1. Role of Phone Interview

The telephone interviewer plays a critical role in the collection of information for the WHI study. In most instances, she (or he) is the woman's first "live" contact with WHI and sets the tone for the entire study. The interviewer's ability to develop and maintain a positive rapport with the woman influences initial recruitment, the quality of the data obtained, and the willingness of the woman to remain in the study for the duration. It is important that you always maintain a professional and friendly manner at every contact with the woman.

3.5.2.2. Eligibility Phone Screen Script

Refer to the scripts provided with the form instructions for *Form 3 – Eligibility Phone Screen* (see *Vol. 3 – Forms, Form 3 – Eligibility Phone Screen* Instructions, Part D – Scripts). The scripts have sufficient detail to explain the study and screen out those women who are unlikely to take part in the study or who would be eliminated because of specific exclusion criteria. Interviewers should try to follow the suggested scripts but modification due to individual CC screening design and clinic flow is appropriate. Interviewers may answer general questions but should refer women to the CC staff during SV1 for additional questions.

3.5.2.3. Determine Preliminary Eligibility

See scripts in *Form 3 – Eligibility Phone Screen* Instructions, Part D – Scripts. If eligible, schedule an initial screening appointment. Not that usually a woman must be eligible for at least on CT component to be scheduled for an SV1. If a CC needs additional women to meet their OS goals, women eligible for OS but not CT may be invited to SV1.

3.5.2.4. Edit the Eligibility Phone Screen

It is critical that *Form 3 - Eligibility Phone Screen* is carefully reviewed immediately following the interview. Quickly check the entire form, making sure that each answer is fully recorded. Edit the interview form as if no future opportunity will be available to clarify a response.

In completing the encounter, the woman's initial eligibility for the CT can be determined. Some specific eligibility criteria, such as participation in other studies, may require further investigation. Update this information and indicate any change in the margin area of the form. Initial any changes in the margin area. Complete all of these items before sending the form to data entry.

3.5.2.5. Process the Eligibility Phone Screen

Sort the completed *Form 3 – Eligibility Phone Screen* forms into the following categories:

- Possibly Eligible: First screening visit scheduled.
- Ineligible. Indicate in the comments area on the form that the woman is ineligible was why and the date of recontact if planned.

Send the forms in all three categories to data entry. Priority for key-entry should be given to the "Possibly Eligible" category first, and then "Ineligible." For women to be contacted at a later date, the interviewer should keep the forms filed according to month or year of planned recontact. On each *Form 2/3 – Eligibility Screen*, enter the name and contact information of the woman, if not previously entered. Scan the *Form 2/3 – Eligibility Screen* (key-enter the Spanish version) and run an eligibility determination for both HRT and DM. (See *Vol. 5 – Data System, Section 7 – Data Entry* for details.)

If the woman has been scheduled for an SV1 and later, the database determines that the woman is ineligible for both components, indicate this change on the form and return the form to the interviewer. The interviewer will then call the woman and cancel her CC visit. This should happen infrequently.

If the database indicates that more information is needed to determine the woman's eligibility for either HRT or DM, schedule an SV0 or SV1, depending on your CC's procedures. If a visit has not been scheduled, indicate the need for an SV0/SV1 on the form and return the form to the interviewer for visit scheduling. Label a temporary folder with each eligible woman's full name. File the interest survey prescreen or postcard and *Form 2/3 – Eligibility Screen* in the temporary folder.

If the database indicates that a woman is ineligible for either HRT or DM, review the reason for exclusion to determine whether this is a temporary or permanent exclusion. See *Section 4.5.4.2. – Ineligible on Form 2/3 – Eligibility Screen* for list of criteria for which you may rescreen.

File the participant's forms according to month and year to re-contact. Forms for women who are permanently excluded should be filed by ID number or alphabetically.

3.5.3. Eligibility Screens Administered Other than by Phone

Clinical Centers need to adapt the approach for telephone screening above to group or individual SV0 settings. The script that accompanies *Form 3 – Eligibility Phone Screen* serves as a model for determining what information should be provided to women in these settings. If the screening activities are conducted in a visit format, other steps, such as completion of other forms (e.g. the *FFQ*) may be carried out at the same SV0 encounter.

Form 2 – Eligibility Screen may be mailed to potential participants. If *Form 2* is mailed include the instruction sheet "How to Fill Out Form 2 – Eligibility Screen", *Figure E.2.4.*, in the packet. Generally, the women will have responded to an initial contact letter by returning a postcard or interest survey or contacted the CC by phone in response to news or publicity. *Form 2 – Eligibility Screen* and *Form 20 – Personal Information* can be mailed together to establish initial eligibility and gather contact information. Clinical Centers may want to include the *FFQ* in this packet to further establish eligibility for DM, improve the yield of SV1 and increase the efficiency of the screening process. A letter of explanation and instruction should accompany he forms along with a #2 pencil and postage-paid return envelope. A special warning against folding the mark-sense version of forms should be stressed. When these forms are received by the CC, the forms should be scanned (and key-entered) so that an eligibility determination an be run. If the woman is eligible, she should be scheduled for an SV1.

3.6. Mailing Initial Baseline Forms

After completing a *Form 3 – Eligibility Phone Screen* or receiving a *Form 2 – Eligibility Screen* and determining that the woman is interested and eligible, CCs may choose to mail the *FFQ* and *Form 20 – Personal Information* to her, if they have not already been completed.

3.6.1. Initial Baseline Forms

Mail the following baseline forms:

- *Form 60 – FFQ*

  The *FFQ* is used as a screening tool to disqualify those women consuming <32% of their kilocalories as fat from the DM component, but must be completed by all women at baseline.

- *Form 20 – Personal Information*

- Other Baseline Forms

  At CC discretion, *Form 30 – Medical History, Form 31 – Reproductive History, Form 32 – Family History*, and *Form 34 – Personal Habits*, or some subset of these, may also be given to the woman to complete before SV1. For CC hosting group SV0s, it may simplify data flow and tracking to administer these baseline forms at one time. For other CCs that have not yet had a face-to-face encounter with the woman, it may be desirable to postpone this data collection until the woman is more heavily committed to the study and has had a chance to develop some rapport with staff. *Form 37 – Thoughts and Feelings* contains sensitive questions and should not be distributed until rapport is established.

3.6.2. Procedures for Mailing and Processing Initial Baseline Forms

Include the following in the packet of materials in a large outgoing envelope:

- Cover letter of welcome.
- *Form 20 – Personal Information*
- *Form 60 – FFQ*
- *From 61 – How to Fill Out the Food Questionnaire*
- A general instruction sheet for completing forms.
- One #2 pencil.
- A large return-addressed envelope with postage prepaid, if you choose to ask the woman to return the *FFQ* to the CC by mail for evaluation of dietary eligibility before SV1.

If an appointment for SV0 or SV1 has already been made include:

- Appointment reminder.
- Map and directions to the CC.
- Information about parking.

Label the packets. Mailing labels may be generated for mailing the packet to the identified group of participants who are interested and eligible for study participation. (To reduce the chance of having the wrong participant label on forms, it is recommended that the participant barcode ID labels **not be attached** to forms until they are returned.)

Mail the baseline forms packet to women who are eligible and interested as determined by completion of *Form 2/3 – Eligibility Screen*. Mail the packet immediately after the telephone contact. Because the *FFQ* is scannable and must not be folded, large envelopes are needed so it can be kept flat.

Process returned questionnaires. Open each returned questionnaire packet as it is received. Stamp the date received on it. Pull the woman's temporary folder. Place a participant barcode label on each form where indicated.

Review each form for completeness and readability. Review the *FFQ* according to the procedures of *Section 10.2.3.2. - Pre-Scan Edit*. Scan the form into the database. Run an eligibility determination for both HRT and DM. If CCs choose to ask women to return the *FFQ*s to the CC by mail before scheduling an SV1, the eligibility determination for DM should be made before scheduling the visit. CCs may thereby reduce the number of CC visits scheduled for women ineligible for the DM. If the woman is ineligible for **both** the CT components indicate this in her temporary folder. At CC discretion, contact the woman by phone or send her a letter of regret thanking her for her time thus far and indicating that she may be eligible for the OS if she is interested. If more information is needed to determine eligibility for **either** CT component, contact the woman and schedule an SV1.

If a CC has an abundance of women eligible and willing to proceed with SV1, give priority to those willing and eligible for both HRT and DM. In planning the study, certain assumptions were made about the overlap between these components. To maintain the desired efficiency in operations and cost, it is important to recruit for this overlap as often as possible. Experience gained early in the recruitment process will help determine if there are other ways to facilitate the overlap.

Proceed with preparation for SV1 as described in *Section 4.2.3. - Preparation for SV1*.

3.7. Visit (SV0) (Not Required)

The purpose of SV0 is to provide a clear explanation of WHI, to determine preliminary eligibility, and to schedule and SV1.

The SV0 can be designed for a variety of uses. It can be used for orientation and baseline screening for potential participants or, for example, streamlines for women interested in HRT and needing a hormone wash-out. SV0 groups can average from 10 to 40 or more women depending on the SV0 design or staff and facilities available. An SV0 can be held at the CC or in the community. Some community organizations, such as churches or women's groups, etc., will sponsor SV0s at their facilities. See *Table 3.1. – Possible Pre-SV1 Recruitment Contacts* for SV0 options used at various CCs. Two possible SV0scenarios are described below.

Scenario 1:

The baseline screening type SV0 begins with staff and potential participant introduction. Women enjoy learning about each other during this time and can share reasons why they are interested in the study. Next is an informational presentation that can include an orientation video or a verbal overview of WHI, including a description of study components and the commitment requirements of each component. A question-and-answer period follows the informational presentation to create a less formal atmosphere and to make sure the women fully understand the study. The first half of the SV0 ends with the completion of *Form 2 – Eligibility Screen* which the staff review on the spot to determine completeness and preliminary eligibility. The first part generally takes about one hour.

After a refreshment break, the second hour begins with completion of the Initial Informed Consent form. If the woman signs it, she is given a copy to keep. Women are also encouraged to take the consent form home to read at their leisure and return at the SV1. The *FFQ* can follow the consent. As the *FFQ*s are completed, staff members review them for completeness and clarify any omissions or mistakes immediately. The *FFQ*s can be scanned at this time if the scanner is available to determine DM eligibility and guide subsequent screening activities. However, scanning immediately can be very time consuming depending on the number of women present and the number of staff available. You may need to postpone review of the *FFQ*s to the next day and phone women for clarification of problems. *Form 20 – Personal Information* can be completed at this time or given to the woman to complete at home and bring to the SV1. An appointment for SV1 is made if the *FFQ* is reviewed at the end of the SV0, taking into account any preliminary eligibility determination.

Scenario 2:

Another scenario is to invite women to an SV0 after they have returned a completed *Form 2 – Eligibility Screen* in order to complete the *FFQ* and *Form 20 – Personal Information*.

Initial contact with a potential participant follows a mailing or media event. A *Form 3* has been completed over the phone or *Form 2* has been mailed and returned. Initial eligibility has been determined. An SV0 appointment confirmation letter, map, and the *FFQ* and *Form 20 – Personal Information* have previously been mailed to the woman and she brings these with her to the SV0.

The woman signs in at the reception desk, turns in her completed *FFQ* and *Form 20 – Personal Information*, receives a folder containing a welcome and agenda page, fact sheet, participant feedback form *Initial Informed Consent* to take home for informational purposes, and a name tag. The nutritionist does a cursory review of the *FFQ* and has the woman complete unanswered questions. The nutritionist or data coordinator then scans the *FFQ* into the computer.

A 30-minute presentation by CC staff uses an introductory video and slides of the staff, clinic, and the nutrition site. Following a question-and-answer session, the CC staff (2-3) speak individually to women to assess their interest and inform them of their eligibility status. An SV1 is scheduled for interested and eligible women. Hormone "washout" letters are given to interested women currently taking hormones to take to their physicians. Participant feedback forms are collected.

Cancellations and reschedules for SV0s should be recorded and tracked.

Table 3.1
Possible Pre-SV1 Recruitment Contacts

Options	Contact 1	Contact 2	Contact 3
1	Form 3	SV0: FFQ Completed, Scanned	SV1
2	Form 2 & FFQ Mailed	Form 2 & FFQ Scanned	SV1
3	Form 3	FFQ Mailed	SV1: FFQ Scanned
4	SV0: Form 2, FFQ Taken Home	SV1: FFQ Scanned	

Figure 3.1.
WHI Logo and Catch Phrase

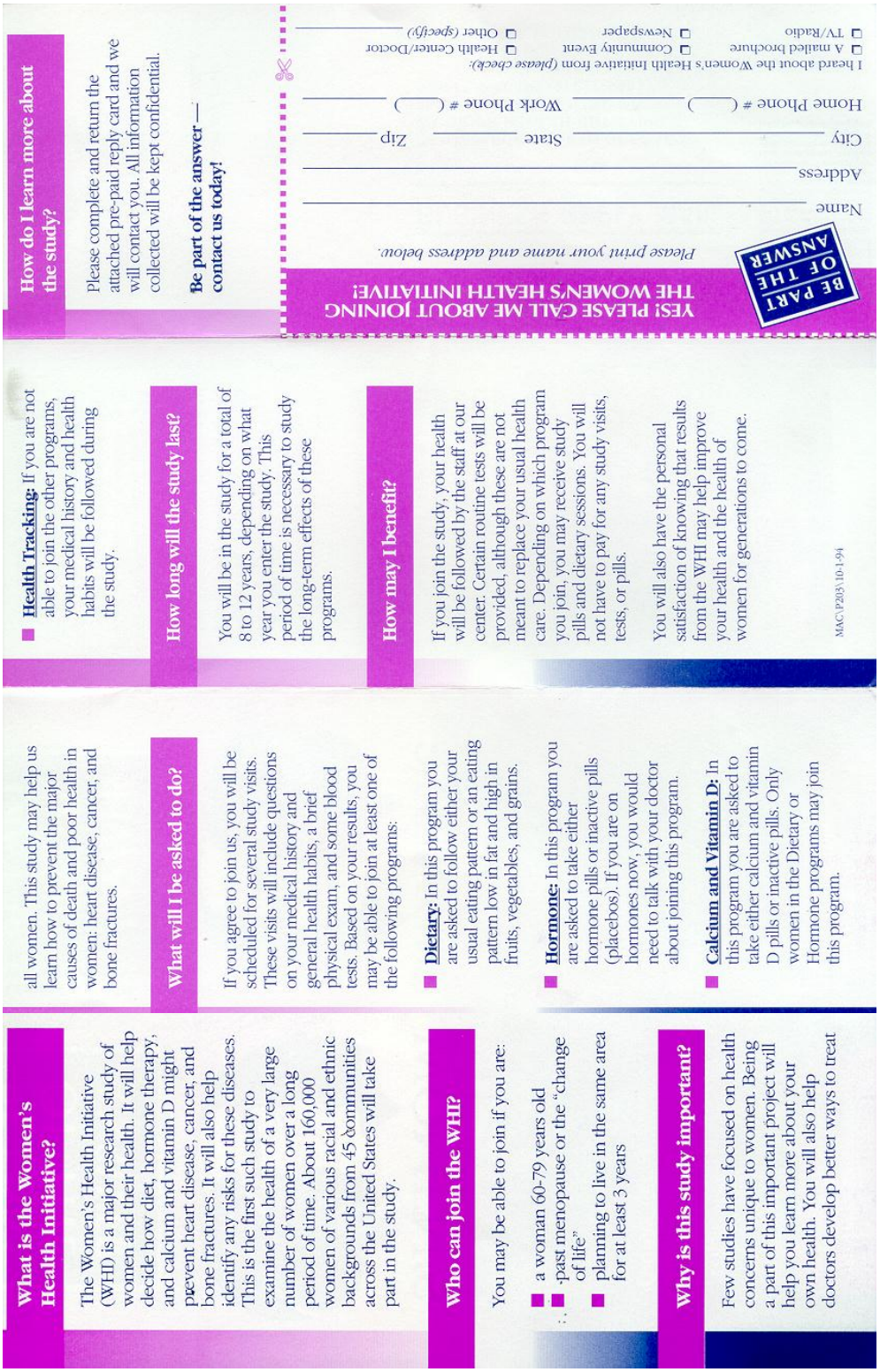
WHI Logo

WHI Catch Phrase

"Be Part of the Answer"

Figure 3.2.
WHI Recruitment Brochure

Figure 3.2.
WHI Recruitment Brochure
(Continued)



Section 3
Recruitment

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SECTION 4

SCREENING

INTRODUCTION

The Women's Health Initiative (WHI) screening program determines the eligibility and interest of an identified woman for each of the study components and obtains baseline measures for each participant. Women are screened if they have expressed interest in the Hormone Replacement Therapy (HRT) or Dietary Modification (DM) components, have been prescreened at an initial contact, and continue to be eligible for at least one of these Clinical Trial (CT) components or the Observational Study (OS).

The three screening visits are designed to minimize Clinical Center (CC) workload and participant burden as much as possible. Exclusionary criteria that are likely to apply to many women and procedures that can be obtained at low cost should be assessed early in the process. The evaluation of criteria that would identify only a few ineligible women and more expensive procedures are scheduled later in the process. A goal of the screening program is also to select those women who will likely participate for the length of the study. Ability and willingness to complete the screening requirements should be an indicator of future retention.

The screening process has been designed to allow flexibility for individual CCs to decide how participants will be contacted and when certain tasks will be completed. *Vol. 1 - Table 1-A1.1 - Frequency of Data Collection* identifies the recommended screening visit at which to complete a task.

4.1. Screening Visits for WHI

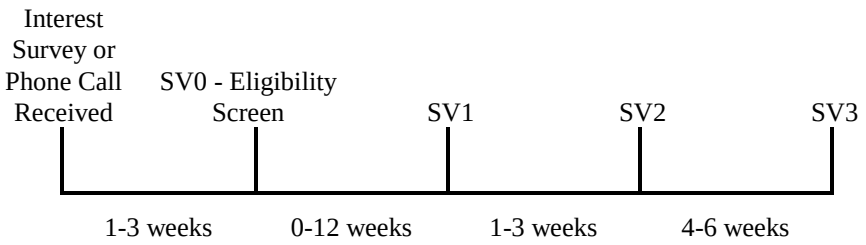
There are three screening visits for the WHI: Screening Visit 1 (SV1), Screening Visit 2 (SV2), and Screening Visit 3 (SV3). CCs complete one prescreening contact (Screening Visit 0 or SV0) via phone, mail, or a visit, at which the woman is asked to complete *Form 2/3 - Eligibility Screen* and other activities at CC discretion. (See *Section 3.7 - Visit (SV0)* for description of SV0 contacts.)

Women will be introduced to the CT components or the OS during the screening visits. These visits are critical to ensure that only fully informed, eligible, and highly motivated women are randomized into the CT or enrolled into the OS. The three screening visits serve to:

- Fully inform potential participants of the requirements, procedures, risks, and benefits of the CT and OS.
- Collect data to establish baseline information and to determine eligibility.
- Identify participants who will be highly motivated to continue in the CT or OS.
- Establish relationships and rapport between the participant and CC staff to promote continued interest and retention in the study.
- Randomize participants into the CT or enroll them into the OS.
- Dispense HRT enrollment pills at SV2 and study pills at SV3.
- Assign a participant to a DM intervention group once she has been randomized, if appropriate.

The scheduling of screening visits conforms to the pattern shown in *Figure 4.1 - Recommended Time Between Screening Visits.* Preferably, the interval between SV0 and SV1 will be no longer than four weeks. However, since the date of SV3 will become the target date for the annual visit, the SV3 date should not be scheduled at times that a participant is known to be unavailable every year. The interval between SV0 and SV1 will also be prolonged if a hormone washout is necessary. For HRT participants, the minimum time between SV2 and SV3 is 28 days to allow for the enrollment pill period. The interval between SV2 and SV3 may be shorter for women interested in and eligible for DM only. Participants who do not complete all screening activities between SV1 and SV3 within six months (with a few exceptions as noted in *Section 4.5.3 - Time Limits During Screening*) must repeat those activities over six months old.

Figure 4.1
Recommended Time Between Screening Visits



The content of the screening visits overall must follow the *WHI Protocol (Vol. 1, Section 1)*. However, CCs may rearrange the activities within a screening visit or move activities to earlier or later screening visits to better fit the flow of the particular CC, as long as the arrangement meets specific requirements given in this manual. *Vol. 1 - Section 1-A1, Protocol, Appendix 1* shows the recommended screening visit by which you should perform an activity. No procedures or data collection may be done until the participant has signed the appropriate consent forms.

General limitations on flexibility in the content of the screening visits include the following:

- Sign the *Initial Consent* before completing activities at SV1.
- Measure blood pressure before drawing the blood sample, if possible, or perform the blood draw at least 30 minutes after the blood pressure measurement in the opposite arm.
- Collect the blood sample as early as possible at the visit, since the participant will be fasting, and provide a snack after the blood draw.
- If the participant is not fasting at SV1, collect the blood sample at SV2. If the participant is not fasting at SV2, schedule another time to obtain a fasting blood sample.
- Sign the *HRT Consent* before dispensing HRT enrollment pills at SV2.
- Allow at least 28 days between SV2 and SV3 for HRT participants.
- Complete screening, SV1 through randomization (at SV3), within six months (see *Section 4.5.3 - Time Limits During Screening*).*
- Complete forms and procedures required for the OS at SV1, if possible. Otherwise, OS participants may require an additional visit.

Figures 4.2 to *4.7* give an overview of each of the three screening visits, the specific tasks, and the estimated time to complete the task (for both CC staff and participants). *Sections 4.2* to *4.4*, and *4.6* describe the activities of the SV1, SV2, and SV3 in detail and follow the flow depicted in *Figure 4.3, Figure 4.5* and *Figure 4.7*.

In general, all visits contain similar activities in terms of preparation for the visit, greeting the participant, reviewing self-administered forms, performing the various activities of the visit, providing the participant with appropriate materials before she leaves, and scheduling the next visit. Since the visits contain many different activities and the participant will most likely be seen by several different CC staff, it is helpful to have one CC staff person oversee the participant's progress through each screening visit. It is useful to have a visit-specific checklist for following the participant through the various activities and ensuring she completes them. *Model Screening Visit Checklists* in *Appendix E* provide a list of tasks to complete and check off at each of the three screening visits. (Computer files of these models are available from the Clinical Coordinating Center (CCC) upon request.)

* *Note:* HRT or HRT/DM participants may have their screening time extended if a six month follow-up mammogram is needed to determine eligibility.

Figure 4.2
Estimated SV1 Activity Times
(*Note*: Screening Visit scenarios may vary across CCs.)

Screening Visit 1	Minutes (Staff)	Minutes (Participant)
Send *Form 60 - FFQ, Form 61 - How to Fill Out the Food Questionnaire,* and *Form 20 - Personal Information*	4	—
Complete *Form 60 - FFQ* and *Form 20 - Personal Information* at home or in CC	—	60
Reception	5	5
Offer and Show WHI Consent Video	1	10
Discuss *Initial Consent*/General Medical Release and obtain signatures	15	15
Complete *Form 11 - Consent Status*	1	—
Review questionnaires/scan *Form 60 - FFQ*	5	5
Form 80 - Physical Measurements (height, weight, waist and hip measures, resting pulse, 2 blood pressure measurements)	20	20
Fasting blood draw	15	10
Task 44 - Current Medications	5	5
Task 45 - Current Supplements	5	5
Form 43 - Hormone Use	15	10
Blood processing*	20	—
Freeze and ship blood samples*	10	—
Detailed description of CT and OS (including videos)*	20	20
Distribute *Form 30 - Medical History Questionnaire* and *Form 31 - Reproductive History Questionnaire*	2	2
Schedule second screening visit	5	5
Determine eligibility and complete screening visit checklist	5	—
Code, scan, and key-enter forms	15	—
Exit interview/referrals	10	10
<u>OS Participants</u>:		
OS information, consent, and enrollment	15	15
Form 42 - Observational Study Questionnaire and remaining baseline CT forms	5	60-75
<u>For Bone Densitometry CCs</u>:		
Bone densitometry	25	20
Urine samples (including collection, packaging, and shipment)	10	5
Totals**	3 hours 15 minutes - OS 3 hours - CT	4 hours 15 minutes - OS 3 hours - CT

* This can be done in batches (e.g., several women's blood samples).

Figure 4.3
Overview of SV1 (Recommended)

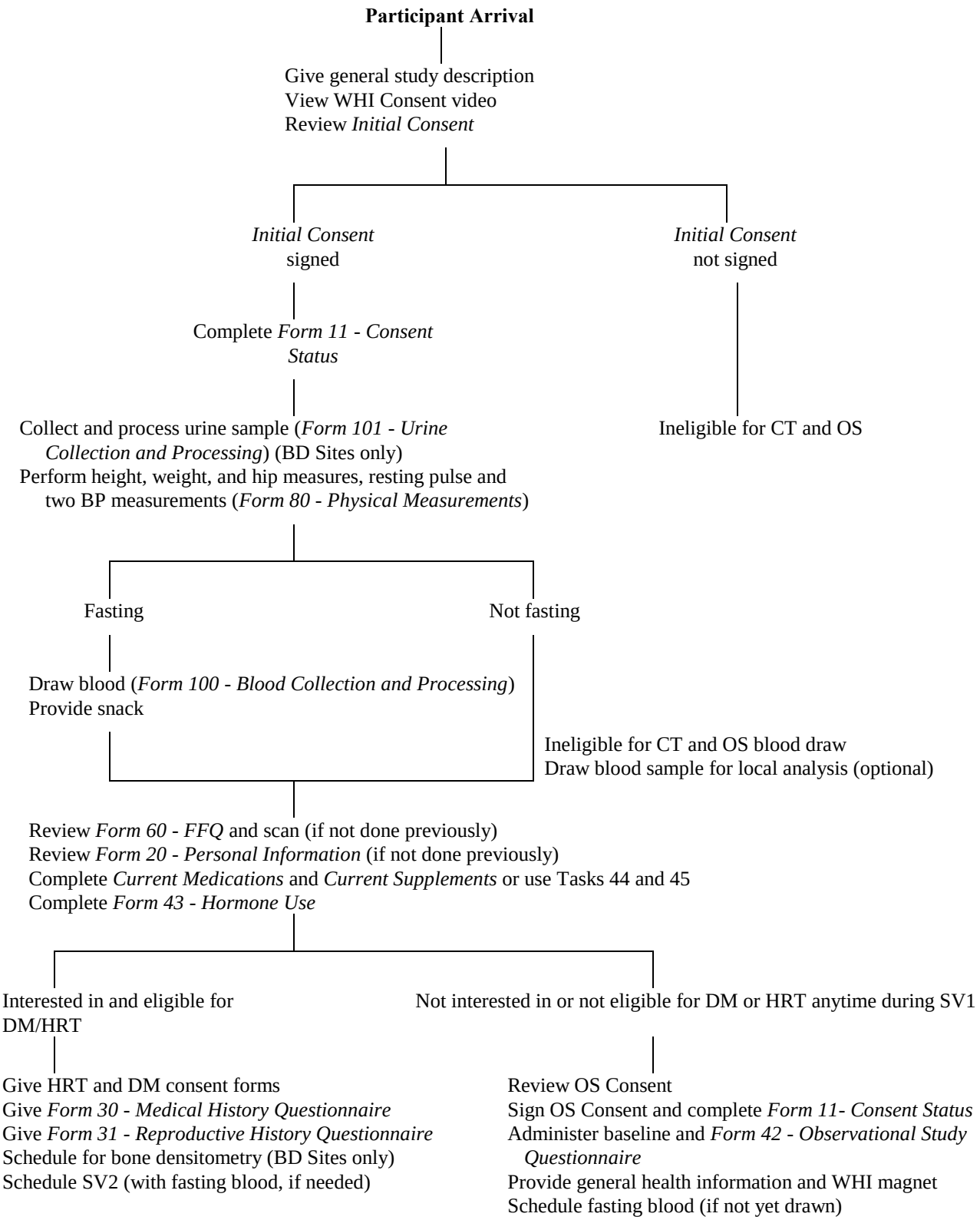


Figure 4.4
Estimated SV2 Activity Times

Screening Visit 2	Minutes (Staff)	Minutes (Participant)
Complete *Form 30 - Medical History Questionnaire* and *Form 31 - Reproductive History Questionnaire* (at home or in CC)		30
Reception	5	5
Review self-administered forms	5	5
CT consent form(s) signed	15	15
Review and enter complete blood count results (and triglycerides, if appropriate)	10	5
Form 86 - ECG	15	15
Form 84 - Clinical Breast Exam	10	10
Breast self-exam teaching (video optional)	10	10-15
Schedule mammogram appointment (or request mammogram results, as appropriate)	10	5
Form 81 - Pelvic Exam (HRT)	15	15
Form 92 - Pap Smear (or request Pap smear results, as appropriate) (HRT)	5	5
Form 82 - Endometrial Aspiration (HRT with uterus)	20	20
Dispense enrollment pills (HRT)	5	5
Form 53 - HRT Calendar instruction (HRT with uterus)	5	5
HRT Handbook review	10	10
Form 62 - 4DFR (DM) instruction*	30	30 - 40
Distribute *Form 32 - Family History Questionnaire*, *Form 34 - Personal Habits Questionnaire,* and *Form 37 - Thoughts and Feelings*	2	2
Determine eligibility and complete screening visit checklist	5	—
Code, scan, and key-enter forms	15	—
Exit interview/referrals	10	10
Schedule third screening visit	5	5
<u>OS Participants</u>:		
OS information, consent and enrollment	15	15
Form 42 - Observational Study Questionnaire and remaining baseline CT forms	5	60
Totals	1 hour 30 minutes - OS 3 hours 30 minutes - HRT+DM** 3 hours - HRT 2 hours 30 minutes - DM	2 hours 30 minutes - OS 3 hours 30 minutes - HRT+DM 3 hours - HRT 2 hours 30 minutes - DM

* As much as possible, this should be done in groups of women to minimize staff time.

Figure 4.5
Overview of SV2 (Recommended)

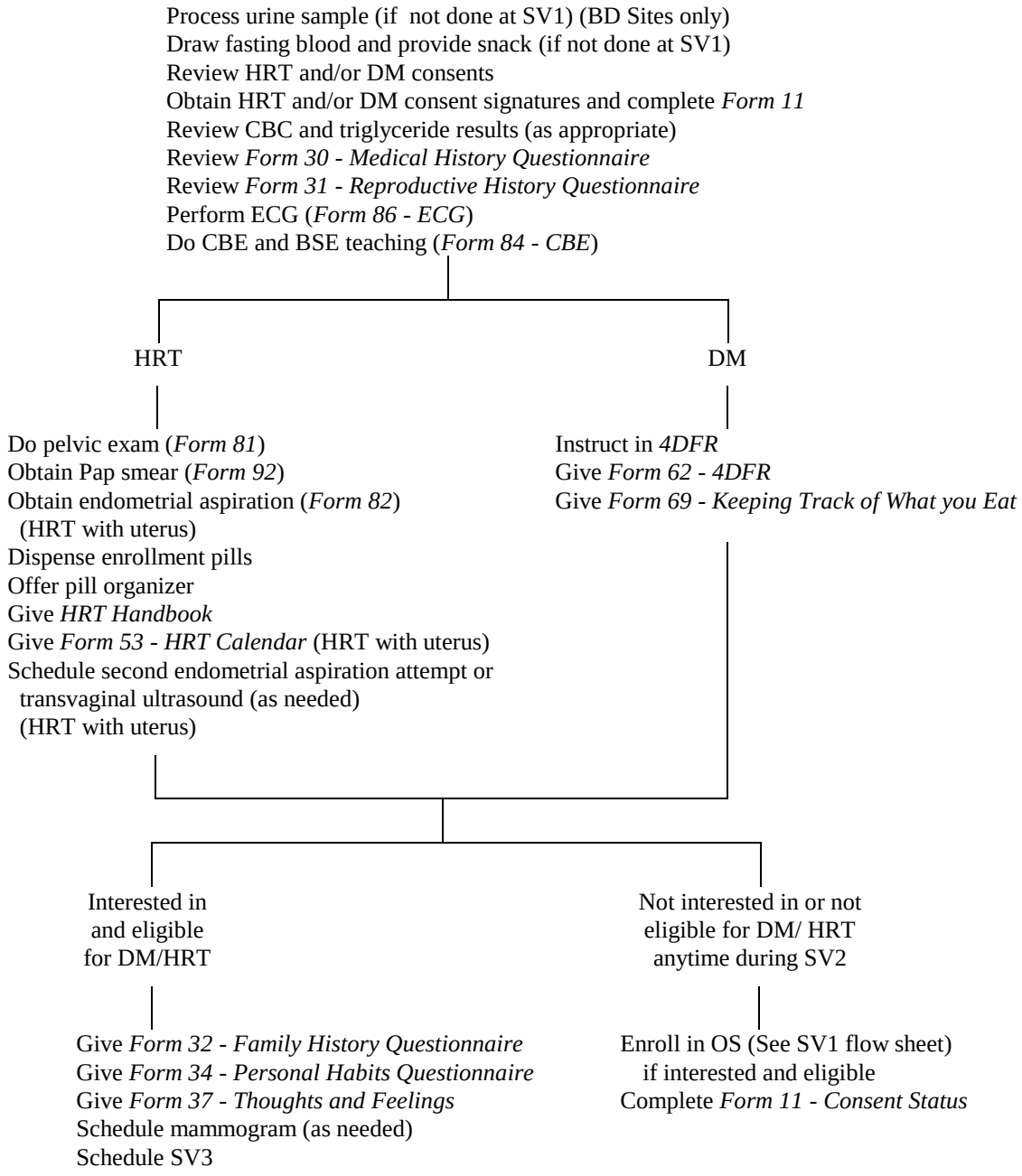
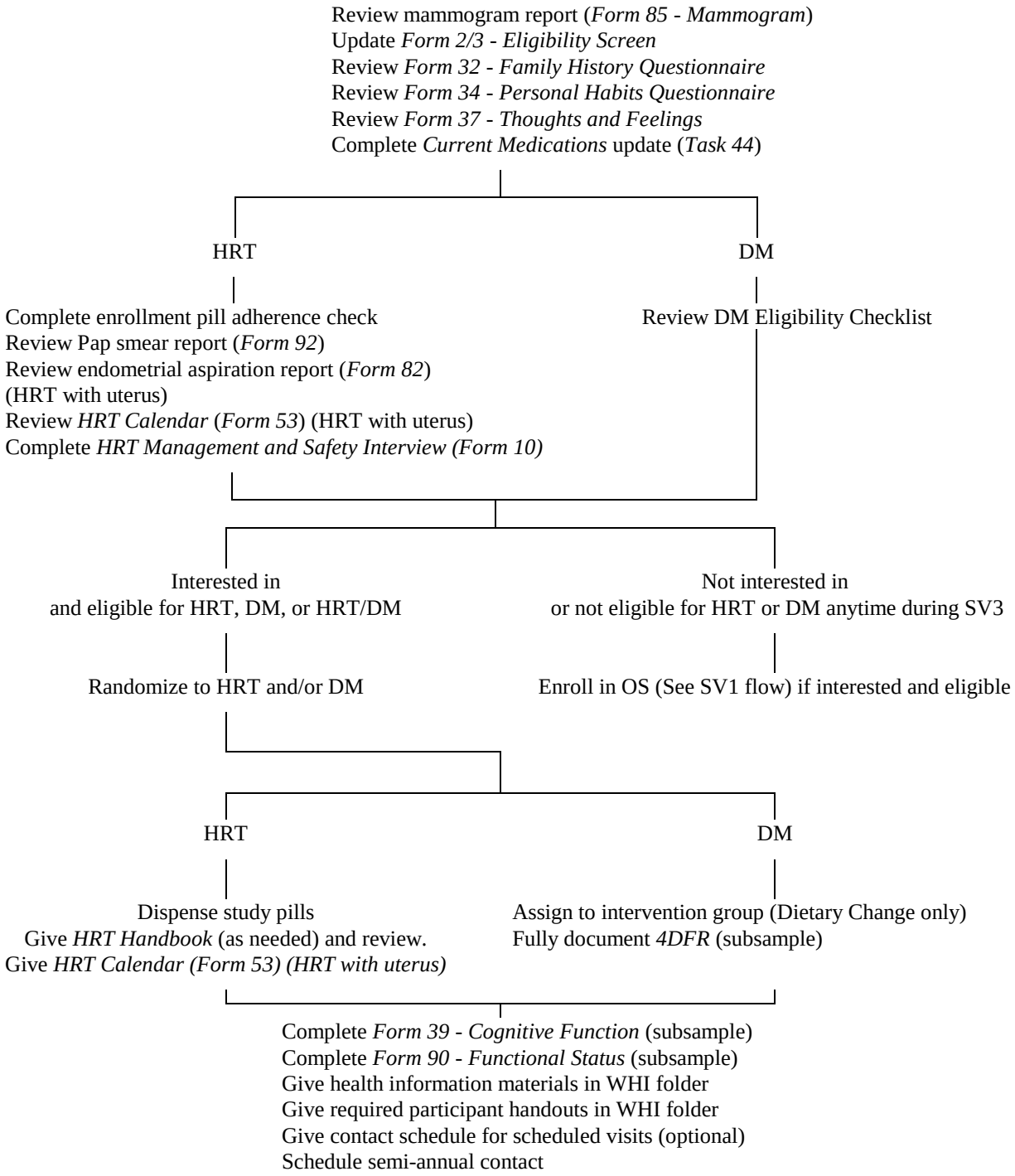


Figure 4.6
Estimated SV3 Activity Times

Screening Visit 3	Minutes (Staff)	Minutes (Participant)
Complete *Form 32 - Family History Questionnaire, Form 34 - Personal Habits Questionnaire,* and *Form 37 - Thoughts and Feelings* (at home or in CC)		60
Reception	5	5
Review mammogram results (*Form 85*)	10	5
Update contact (*Form 20*), medication (*Form 44*), and eligibility information (*Form 2/3*)	10	10
Review DM Eligibility Checklist (DM)	30	30
Review remaining self-administered forms	2	2
Assess enrollment pill adherence (weigh pills) (HRT)	10	5
Review Pap smear (*Form 92*) & endometrial aspiration (*Form* 82) results (HRT with uterus)	10	5
Review *Form 53 - HRT Calendar* (HRT with uterus)	10	10
Complete *Form 10 - HRT Management and Safety Interview*	5	5
Determine eligibility and complete screening visit checklists	5	—
Code, scan, and key-enter forms	10	—
Randomization - identification of subsamples	15	—
Dispense study pills and *HRT Handbook* (if needed) (HRT)	15	10
Give a new *Form 53 - HRT Calendar* (HRT with uterus)	2	2
Assign dietary groups (DM)	10	10
Document *Form 62 - 4DFR* (DM) (subsample)	45	45
Form 39 - Cognitive Function (subsample)	15	15
Form 90 - Functional Status (subsample)	15	15
Exit interview	15	15
<u>OS Participants</u>:		
OS information, consent, and enrollment	15	10
Form 42 - Observational Study Questionnaire	5	15
Totals	45 minutes - OS 2 hours 30 minutes to 3 hours 45 minutes - HRT & DM 1 hours 45 minutes to 2 hours 35 minutes - HRT 1 hour 50 minutes to 2 hours 35 minutes - DM	2 hours - OS 2 hours 45 minutes to 4 hours - HRT & DM 2 hours to 2 hours 40 minutes - HRT 2 hours 10 minutes to 3 hours - DM

Figure 4.7
Overview of SV3 (Recommended)

Participant Arrival
HRT and DM



4.2. SV1

The recommended and required procedures for SV1 should minimize the participant's time burden and assure that baseline measurements and eligibility are determined appropriately.

Each CC can organize the flow of SV1 to fit its needs as long as the flow meets the requirements below. Once established, the flow within each CC should be consistent for all SV1s conducted at that CC.

- Describe the overall study and participation expectations before signing the *Initial Consent*.
- Obtain a signed *Initial Consent* before collecting additional information or performing further procedures. The *Initial Consent* must include all SV1 procedures conducted at your CC.
- Limit the time required of the participant during the visit to no more than 4½ hours when possible.
- Complete *Form 60 - Food Frequency Questionnaire (FFQ)* and *Form 20 - Personal Information* before other SV1 activities are done (if not collected before SV1).
- If a participant decides at any time that she does not want to be part of either the CT or the OS, then all activities should stop for her at that point. She should be thanked cordially for her time, and invited to call the CC again if she wishes any further information about the study. Complete *Form 11 - Consent Status*. If she requests that her forms be returned, try to accommodate this request by providing all self-administered forms, whether data-entered or not.

It is recommended that the participant should not wait more than 10 minutes past her appointment time to be seen by CC staff.

4.2.1. Purpose of SV1

The purpose of SV1 is to:

- Establish rapport with the participant and promote further interest in the study.
- Inform the participant about SV1 activities.
- Obtain initial consent for the screening procedures in SV1.
- Screen for exclusion criteria.
- Confirm eligibility and willingness to participate.
- Obtain baseline data and collect baseline specimens and measurements.
- Fully inform the participant of the CT and OS.
- Obtain consent for OS participation (if appropriate).
- Schedule the next screening contact.

The SV1 is one of the first steps in the WHI study enrollment process and may be a woman's initial contact with the WHI CC. Impressions left by the WHI CC staff can influence the woman's decision to join the study. Additionally, the SV1 might be the only personal contact with some OS participants for three years. General strategies for creating and maintaining good impressions with the participants are described in *Section 17.1 - General Activities to Promote Retention.*

The SV1 is challenging to the CC because:

- The staff need to convey a professional, friendly attitude while providing accurate information in response to spoken and possible unspoken questions.
- Each staff member needs to establish rapport with the participant and provide information about each procedure performed.

- Each staff member needs to be fresh and enthusiastic about WHI with each participant.
- Staff members' personal biases about particular WHI components (e.g., favoring one component over another) must remain unspoken so that the woman can make her own informed decision about participating.

The SV1 is important for establishing rapport and bonding with the participant. Optimal times for building rapport include the beginning of SV1, when the overall description of the study is given, when the CT components or the OS are explained in detail, and at the end of the visit. You might tell the participant that she is not only an important person to the CC but that she is also a participant in an important nationwide study of women. Thank the participant for her time. All procedures should be conducted in a professional and caring manner.

4.2.2. Activities During SV1 (Recommended)

A suggested scenario for SV1 is described below. Some alternatives to this scenario are identified in parentheses, although all activities must be completed at some time during the screening process. (See *Vol. 1, Table 1-A1.1 - Frequency of Data Collection* for the suggested visit at which to perform the activities.) During SV1, the CC staff should:

- Describe the WHI components in general terms as well as the specific activities of SV1 (may be accomplished at SV0).
- Show the *WHI Consent Video*.
- Review the *Initial Consent* with the participant, and obtain an informed consent signature (may be accomplished at SV0).
- Obtain a signed *General Medical Release*.
- Collect a urine sample (BD sites only) (may be accomplished at SV2).
- Perform other SV1 measurement procedures (blood pressure, resting pulse, height, weight, waist and hip measurements). (Note that for CT participants, waist and hip circumferences may be done at SV2 when the ECG and CBE are usually done.)
- Review the returned self-administered questionnaires (*Form 60 - FFQ* and *Form 20 - Personal Information* completed at home or on-site) and discuss specific questions with the participant (may be done at SV0).
- Scan *Form 60 - FFQ* (may be done at SV0).
- Perform venipuncture, blood processing, and, for HRT participants, visual inspection for triglycerides (may be done at SV2 if the participant is not fasting at SV1).
- Provide a snack to the participant after the blood draw.
- Complete *Current Medications* and *Current Supplements* review (Tasks 44 and 45) to collect baseline data on prescription medications; over-the-counter medications; and vitamin, mineral and bulk fiber supplements (this may be accomplished at SV2).
- Make a decision to continue screening for the CT based on current eligibility determination (decision algorithms are computerized).
- Administer *Form 43 - Hormone Use* interview.
- Explain the CT in detail to participants who are still interested.
- Give the interested participant a packet to take home with her that will include:
    a) Clinical trial consent forms (HRT and/or DM).
    b) *Form 30 - Medical History Questionnaire* and *Form 31 - Reproductive History Questionnaire.*

- Schedule bone densitometry (BD sites only).
- Schedule an appointment for SV2 for participants who continue to be eligible for and interested in the CT.
- Describe the OS if the participant is not interested in or eligible for the CT.
- For participants in the OS who were not fasting at SV1, arrange for a return visit for a blood collection.
- Review the *OS Consent* and obtain informed consent signature.
- For participants who are interested in the OS, arrange for completion of baseline and OS questionnaires, preferably in the CC. If necessary, let the participant take them home with a postage-paid return mailer.

4.2.3. Preparation for SV1

After completing *Form 2/3 - Eligibility Screen* and being found eligible and interested, a participant is asked to schedule an SV1. (See *Section 3.5 - Screening Contact* for description of *Form 2/3 - Eligibility Screen* administration.) After a participant has completed *Form 2/3*, enter her name and other identifying information into the database and print mailing and barcode labels. (See *Form 2/3 - Eligibility Screen* form instructions in *Vol. 3 - Forms* for details on processing *Form 2/3*.)

Schedule as many SV1s as possible before noon because the participants will need to arrive fasting for a blood draw. The SV1 is usually conducted within four weeks of *Form 2/3 - Eligibility Screen*, but may not occur for up to 12 weeks or more because of personal schedules or the need for a hormone washout period.

4.2.3.1. Two Weeks Before SV1

Each day, determine which potential participants have SV1s scheduled in two weeks and therefore need an appointment reminder letter (see model in *Figure E.3.1 - Sample SV1 Reminder Letter*), questionnaires, and a medication bag. Mail the packets to participants via first-class mail (see *Section 3.6 - Mailing Initial Baseline Forms*). Remind participants to:

- Bring the completed questionnaires and all of their prescription medications (including all hormone medications); currently used over-the-counter medications; and any vitamins, minerals, or bulk fiber supplements with them in their original bottles to SV1.
- Take no aspirin or non-steroidal anti-inflammatory drugs (NSAIDs like ibuprofen, Advil®, or Motrin®) for 48 hours before the visit (but take all regular morning medications except oral hypoglycemics or insulin). *Note*: NSAIDs that are taken <u>regularly</u> may be continued and taken within the 48 hours before the blood draw, consistent with the participant's usual schedule. Participants on oral hypoglycemics or insulin should hold their usual morning dose unless instructed otherwise by a physician.
- Eat nothing, drink only water, and refrain from vigorous exercise during the 12 hours before the CC visit.
- Not smoke for one hour before the blood draw.
- Wear comfortable, light, loose, 2-piece clothing.
- Wear flat, comfortable shoes.
- Bring a first-void urine sample in provided container (BD sites only).

An additional phone call reminder to participants may be made 1 to 3 days before the SV1.

4.2.3.2. One Day Before SV1

Each day, prepare for SV1s scheduled for the next day.

- Pull and review participant files (prepared during SV0 - see *Section 3.5 - Screening Contact*) for each participant scheduled for an SV1 the following day. The file should contain all forms you will use in

SV1, as well as instructional materials and two copies of the *Initial Consent*. The forms should be placed in the file folder in the order you will use them in the visit. It is also useful to have a screening visit checklist on top of the packet of materials. (See model in *Figure E.4.2 - Model SV1 Checklist*.)

- Stock and prepare trays and blood tubes for blood samples to be drawn. (See *Figure 11.2 - Blood Collection and Aliquot Schedule.*)
- Check for other supplies and equipment needed for the various SV1 procedures.

4.2.4. Guidelines for SV1 Activities

Use the screening visit checklist (see model in *Figure E.4.2 - Model SV1 Checklist*) as a guide for completing all the tasks at SV1 (you can obtain an electronic version of this checklist from the VCC). Check off each form or activity on the checklist to indicate if you did or did not complete the task.

4.2.4.1. Reception

When the participant first arrives at the CC for SV1, have her check in at the reception desk. The Receptionist should:

- Locate the participant's file.
- Indicate a comfortable place where the participant may wait until an Interviewer can see her.
- Notify the Interviewer or other appropriate CC staff that the participant is waiting.

The Receptionist may review *Form 20 - Personal Information Questionnaire* for completeness while the participant is waiting. The Interviewer greets the participant in the waiting area and escorts her to the appropriate room. A suggested greeting is:

> "Hello, Ms./Mrs. (individual's name). My name is _____ and I'll be one of the people seeing you today. Thanks for volunteering to come down and hear more about the WHI study. Were you able to find us okay?"

Spouses or other support persons may accompany a potential participant to the interview room and remain through the review and signing of the *Initial Consent Form*. However, they should be asked to wait in the reception area when SV1 physical measurements are begun.

4.2.4.2. General Study Description (Required)

When the participant arrives for the visit, describe the study to her in general terms, focusing on the CT components. At the same time, explain that if she does not enter one of these components, she will be eligible for the OS. A recommended script is provided below:

> "The Women's Health Initiative is a program sponsored by the National Institutes of Health to study the effect of hormone replacement therapy, dietary change, and calcium and vitamin D pills on a woman's risk for heart disease, cancer, and bone fractures (or broken bones). A total of 164,500 women from various backgrounds all over the United States between the ages of 50 and 79 will join the study at clinic sites throughout the US. WHI staff will see if women can join by asking questions about their medical, family, and reproductive history; personal habits; and food habits. They will also measure each woman's height, weight, waist, hip, pulse, and blood pressure; take a sample of each woman's blood; and possibly do other medical tests like mammograms and Pap smears. Women who are able to join may choose to join any or all of the three parts of the study. Women who choose not to join or who are found not to be able to join the studies of hormones or dietary change will be invited to join the Observational Study, the fourth part of the study. Women who participate in any part of the WHI will be in the study for a total of about nine to twelve years, depending on when you join."

Arrange for the participant to watch the *WHI Consent Video* (10 minutes) and review with her the *Initial Consent* for your CC. The study description and video may be done in groups of 8-10 women for efficiency.

4.2.4.3. Initial (Screening) Informed Consent (Required)

a) Description of the WHI Study and Screening Visits

Describe the study and screening procedures in more detail after the video is over. A recommended script is provided in *Figure 4.11 - Initial Consent Script*.

Even if this script is not followed, the following key points must be covered with the participant:

- Her participation is voluntary and she may withdraw at any time.
- Any information she gives will be kept completely confidential and will be released to no one except WHI personnel and, if appropriate, authorized FDA staff.
- Her responses will be added to those of other participants and only composite or grouped information will be released. Neither her name nor any other identifying information will be released in WHI reports or publications.
- A description of the procedures during SV1 at your CC (e.g., pulse, blood pressure, blood draw, height, weight, waist and hip circumference, interviews, and preparation for the next screening visit).
- A description of each procedure and any risks associated:

  Blood draw: "Approximately three tablespoons of blood will be drawn from a vein in your arm. Sometimes a woman may get a bruise at the site of the blood draw or very rarely, an infection may develop at the site where blood was drawn. We will take all possible steps to avoid these problems."

  Height, weight, waist, and hip measurements: "Your height, weight, waist, and hips will be measured over non-binding undergarments and without shoes. There are no risks to these tests."

  Pulse: "Your pulse will be measured for 30 seconds after you have been sitting for five minutes. There is no risk to this test."

  Blood pressure: "Your blood pressure will be measured after you have been sitting for five minutes (or right after the pulse measurement). You will be told your blood pressure reading and whether you need to see your doctor for your blood pressure. There is no risk to this procedure."

b) Requirements of the Initial Informed Consent Process

The *Initial Consent* will cover the procedures and data collection to be performed at SV1.

The WHI CC procedures for informed consent with the participant must meet the following criteria:

- Allow ample time for viewing the *WHI Consent Video*, describing the screening procedures, and answering any questions. The initial consent process may take 15-30 minutes. (*Note:* Much of this may be done in groups.)
- Allow sufficient uninterrupted time for the participant to read the *Initial Consent.* Do not rush or coerce the participant to sign while she is still reading it.
- Review and discuss the *Initial Consent* with the participant. Ask her if she has any questions and answer the questions thoroughly. It may be necessary to read the *Initial Consent* to the participant to increase her understanding.
- The *Initial Consent* is the first form reviewed with the participant at SV1 (with the exception of *Form 20 - Personal Information Questionnaire* or *Form 60 - FFQ* which may be mailed out and completed before SV1).

The content of the model WHI consent forms must be included in all CC consent forms; only wording changes for clarification may be made by the CCs. (See *Vol. 1 - Study Protocol and Policies, Section 2 - Consent Forms* for the *Initial Consent Form.*)

Each WHI CC must also follow the requirements imposed by their own Institutional Review Board (IRB) in carrying out the informed consent procedures. All consent forms used, however, must be reviewed by the NIH Project Office before they will be accepted as WHI consent forms. Submit final, approved consent forms to the CCC for archiving.

c) The *WHI Consent Video* (Required)

Offer all women interested in participating in the WHI the opportunity to view the 10-minute *WHI Consent Video*. The purpose of this video is to inform potential participants about the overall study design and let them know what is expected of participants. The video contains a general description of the study. A brief introduction to the study components is included, including a description of the HRT, DM and CaD trials, and the OS. Screening procedures, the process of randomization, the importance of remaining in the study once enrolled, and the length of enrollment are also discussed.

d) Reviewing the Initial Consent Form (Required)

Review the *Initial Consent Form* with the participant after she has had ample time to read it. Ask her if she has any questions and answer the questions thoroughly.

e) Signing the Initial Consent Form (Required)

Once the participant's questions have been answered, ask her to sign and date two copies of the *Initial Consent* in the appropriate places. Sign two copies of the form yourself, as a WHI representative, and witness and date the form. Give one copy of the form to the participant and file the other in her WHI file. If the participant declines to sign the *Initial Consent*, do no further screening activities and thank the participant for her time. Complete *Form 11 - Consent Status* indicating if she signed or did not sign the *Initial Consent.*

f) Signing the General Medical Release Form

Have the participant sign the *General Medical Release* to obtain appropriate medical records (for results of outside Pap smears, endometrial aspirations, or mammograms; outcome ascertainment; or other information as appropriate). (See a sample in *Figure E.5.1 - Model General Medical Release Form*). Tell her that she may need to sign this form every 6 to 12 months for the study (this will vary by state and institution). If the participant refuses to sign the form, explain to her that this form is to obtain medical records needed to verify eligibility or health information later on. This information will be very important for WHI to get answers to the important women's health questions. Tell the participant that what happens to her is important and the staff will be following her closely for the entire length of the study. Inform the participant that signing the form will in no way change her usual medical care.

4.2.4.4. Blood Draw (Required)

- Draw the participant's blood if she is fasting. If she is not fasting at SV1, make arrangements for a fasting blood draw on or before SV2. (See *Section 11 - Blood and Urine Collection, Processing and Shipping* for instructions on the blood draw and blood handling.) If the first attempt at the blood draw is unsuccessful, the staff person should attempt a second draw. If that second draw is also unsuccessful, another staff member may attempt to draw the participant's blood (for a total of two tries). No more than four blood draw attempts total should be made between two staff persons during a particular visit. At SV2 you must obtain at least enough blood for local lab analysis to evaluate CT eligibility criteria (2 ml of serum) or enough for at least 2 aliquots (4 ml of serum) to be enrolled in OS. (See *Section 11.2.6 - Blood Collection Problems*.)
- During blood processing of HRT-eligible women, inspect the serum for lipemia. (See *Section 4.2.7.1 - Blood Analysis Results*) and *Section 11.3.3 - Processing Samples).* If lipemia is noted, send a blood

sample to your local lab for a determination of the triglyceride level. If you know a participant is not eligible or definitely not interested in HRT, you do not need to do triglyceride testing.

- Give the participant a light snack (e.g., juice, fruit, or crackers) while she is sitting in a quiet, comfortable place, preferably away from the blood-drawing area.

  Serve foods that will help to bring blood sugar back up quickly. Some examples include fruit juices, fruit, granola bars, crackers, English muffins, bagels, or toast (offered with jelly, margarine, or peanut butter).

  Coffee service and snacks made available to participants in the clinic should not convey the impression that the clinic or WHI study promotes food choices that are either low-fat or high-fat. It is acceptable to include moderate or high-fat choices as well as low-fat choices, similar to the acceptable cultural foods of your region. Products with food labels are acceptable, but should not have nutritional claims regarding fat (e.g., low-fat, fat-free, reduced-fat). It would not be appropriate to use a non-dairy creamer that has a fat-free claim on the label. Fat-free creamer dispensed from an unlabeled serving container is appropriate.

4.2.4.5. Questionnaire Review (Required)

Put a participant barcode label on the front page of each completed form in the designated place. (Refer to *Vol. 3 - Forms* for specific instructions regarding the items on each questionnaire.)

a) *Form 20 - Personal Information* (Required)

Review the form if not already reviewed. Be sure that all questions have been answered. Note that it is not absolutely necessary to obtain the social security number if the woman is reluctant to provide this.

b) *Form 60 - Food Frequency Questionnaire* (Required)

If not reviewed and scanned before SV1, review *Form 60 - FFQ*. Probe for additional information about missing answers. Scan the *FFQ* while the woman is still in the CC. WHILMA will indicate if the woman is ineligible for the DM based on her percent calories from fat or total calories. Since completion of 90% of the *FFQ* line items is also a requirement to obtain a reasonable estimate of the woman's diet, WHILMA will indicate if less than 90% of the questions have been answered, in which case the form should be reviewed with the woman. All adjustment questions (pages 2-4) and all summary questions (page 12) on the *FFQ* must be answered. See the instructions for reviewing and editing the *FFQ* in *Vol. 3 - Forms* for more details. Refer to *Section 4.5.4.3 - FFQ Rescreening* for specific information and criteria for completing a second screening FFQ.

c) Eligibility Items

Many of the eligibility items for all components of the WHI were asked on *Form 2/3 - Eligibility Screen.* If not done before SV1, do a preliminary determination of her eligibility. If the form has been entered into the database, you can run an Eligibility Determination (Task 910 and/or 920, as appropriate) to evaluate eligibility at any time. If a participant is on hormone replacement and interested in HRT, hormone washout will be necessary before completing further screening activities (see *Section 5.1.3 - HRT "Washout" Period for Screenees Already on HRT*).

Additionally, eligibility is based on some of the tests and procedures performed during the screening visits. (See *Vol. 5 - Data System, Appendix C.2*. for eligibility mapping to questionnaires and activities.)

If a participant reports any change in the information she previously provided on *Form 2/3* regarding her health or circumstances that now make her ineligible (e.g., subsequent heart attack, cancer diagnosis, intention to move away from the area, recent vaginal bleeding, had a hysterectomy), update her *Form 2/3* as described in the instructions for *Form 2/3* in *Vol. 3 - Forms, Part C - Reviewing and Updating Form 2/3* and run another eligibility determination in WHILMA.

4.2.4.6. Current Medications and Current Supplements Inventory Review (Required)

The purpose of collecting an inventory of current medications and supplements at SV1 is to ensure that a woman is not taking any protocol-excluded medications/supplements and to obtain baseline information. CCs are not expected to monitor a participant's medication and supplement intake for safety concerns during screening, except as defined by WHI protocol for eligibility or local CC guidelines. If CC licensed professional staff (e.g., clinicians or nutritionists) become aware of personal medication intake that is clearly inappropriate, notification of the participant (and her primary care provider, if appropriate) fall within a professional scope of practice.

Ask the participant for her WHI bag containing her medications (including all prescription medications, over-the-counter (OTC) medications, and vitamins, minerals and bulk fiber supplements such as Metamucil®). If she has forgotten to bring them, do the current medications and supplements inventory at SV2.

a) Current Medications

Enter each medication into WHILMA following the procedures in *Vol. 5 - Data System, Section 7.3.1 - Current Medications*. Ask the participant if she is taking any other medications that she did not bring with her. Enter those medications as well. After entering the data, return the bottles to her. Ask the participant to bring any new medications she is prescribed or starts taking during the screening period to the SV3.

Enter OTC medications the participant is currently using, following the same procedures for entering prescription medications. Remind the participant that only OTC medications taken at least twice a week for the preceding two weeks will be entered.

Use *Form 44 - Current Medications (Backup)* for completing the medication inventory if the computer is not available.

b) Current Supplements

Enter each current vitamin and mineral supplement into WHILMA following the procedures described in *Vol. 5 - Data System, Section 7.3.2 - Current Supplements*. Remind the participant only to report current supplements taken at least once a week. The supplement inventory program will offer specific prompts for entering the vitamin formulations when needed. Use *Form 45 - Current Supplements (Backup)* for completing the supplements inventory if the computer is not available.

Eligibility Items:

If a medication is entered into the database that excludes the participant from any component, any subsequent eligibility determination will indicate that the participant is ineligible for that particular component. The medications that exclude a woman are: Heparin, Coumadin, or Warfarin (HRT) and current oral corticosteroids (HRT and DM). Common oral corticosteroid medications are listed below. The most common oral corticosteroids are marked with a star (*).

Oral Corticosteroids

A Hydrocortef	Dexone	Meticorten
Amcort	Duralone	Metrocort
Aristocort	Florinef	M Prednisol
Aristo-pak	Fludrocortisone Acetate	Orasone
Atolone	Haldrone	Paramethasone acetate
Betamethasone	Hexadrol	Pediapred
Celestone	Hydrocortisone	Pre-Dep
Cortef	Hydrocortone	Prednicen-M
Cortisone acetate	Kenacort	Prednisolone
Cortone acetate	Liquid Pred	*Prednisone
Dalalone	Med-Depo	Rep Pred
Decadron	Medralone	Solu Cortef
Deltasone	Medrol: Medrol Dose Pak	SoluMedrol
Depojet	Medrone	Sterapred
Depo-Medrol	Methylpred	TAC-3
Dexamethasone	*Methylprednisolone	Triamcinolone

For HRT, current use of estrogen, progesterone, oral or injectable testosterone (unless the participant goes through a 3-month HRT washout), or tamoxifen also exclude a participant.

4.2.4.7. Physical Measurements (Required)

It is recommended that the baseline anthropometric measures as well as baseline blood pressure and resting pulse be performed at SV1. Resting pulse and blood pressure measurements should be completed before drawing blood or at least 30 minutes after the blood draw. Consult *Section 9 - Clinical Measurements* for the specifics of all physical measurement procedures. Follow the alert protocols identified in that section. CCs may develop a more extensive and conservative set of alert levels for the various tests and procedures in the study.

a) Height and Weight Measurement and Body Mass Index (BMI) Calculation

Record the height and weight in centimeters and kilograms, respectively, on *Form 80 - Physical Measurements*. WHILMA computes Body Mass Index (BMI) from the height and weight measures and uses it to assess eligibility for both the HRT and DM components.

If you wish to determine the participant's BMI before entering the data into WHILMA and running an eligibility determination, you can use the following procedure. To use the BMI nomogram (see *Figure 4.10 - Nomogram for Body Mass Index)*, place a straight-edge ruler between the body weight in kilograms on the left-hand column and the height in centimeters on the right-hand column. Read the BMI at the point where the straight edge connecting height and weight crosses the middle axis. Record the estimate as a whole number on the physical measurements form. Women with a BMI less than 18 kg/m^2 will be excluded from the study. However, the Clinic Practitioner or Lead Nutritionist have an override option for participants with a low BMI. CCs should establish specific criteria for this override. If an estimated BMI is close to the exclusion numbers (that is, between 16–22), you may want to calculate BMI by hand as a cross-check. To do this, use the participant's weight recorded in kilograms, rounding up to the nearest kilogram and height recorded in meters. (Divide the height measurement in centimeters by 100 to get the number of meters.) To calculate BMI:

$$\text{BMI} = \frac{\text{weight (in kilograms)}}{\text{height}^2 \text{ (in meters)}}$$

(1) Multiply the height (in meters) by itself = height^2

(2) Divide the weight (in kilograms) by the answer in #1 (by height^2)

Example: Weight = 75 kg
Height = 170 cm
BMI = $\frac{75 \text{ kg}}{(1.70\text{m})^2} = 26 \text{ kg/m}^2$

The calculated answer should correspond with the BMI from the nomogram. If it does not, check with your supervisor.

b) Waist and Hip Circumference

Neither of these measures will be a basis for exclusion for any of the WHI components. Waist and hip circumference measurements will be measured over non-binding undergarments and may be done when the CT-eligible participant is disrobed for the ECG or clinical breast exam at SV2 or SV3 (depending on your CC's screening scenario), but should be completed at SV1 for participants found at SV1 to be ineligible for CT.

c) Resting Pulse

Measure the radial (or brachial) pulse after the participant has rested for five minutes. Measure the pulse for 30 seconds and record the number you measure on *Form 80 - Physical Measurements*. Then, multiply that number by two and record that result. All follow-up pulse measurements should then also be done on the same side.

Refer participants with a pulse rate greater than 130 beats/minute or less than 40 beats/minute to your Clinic Practitioner for consideration of primary physician referral.

d) Blood Pressure

Measure resting blood pressure in the participant's right arm after the pulse is taken (the opposite side from which the blood is drawn). (In rare cases, it may be necessary to measure blood pressure in the participant's left arm. If you drew blood in the participant's right arm earlier in the visit, use the participant's left arm. All follow-up blood pressure measurements should then also be done on the left arm.) Record two separate measures of systolic and diastolic blood pressure on *Form 80 - Physical Measurements*. Mark "right" or "left" for the arm blood pressure was measured in.

The following blood pressure values will exclude women from the CT, at least temporarily:

Systolic blood pressure > 200 mm Hg

Diastolic blood pressure > 105 mm Hg

See *Section 9 - Clinical Measurements* regarding alert actions for blood pressure readings.

4.2.4.8. Urine Collection (Bone Densitometry Sites)

If your CC is one of the three bone densitometry sites (University of Pittsburgh, University of Alabama, or University of Arizona), collect the first-void urine sample and process according to guidelines in *Section 11 - Blood and Urine Collection, Processing and Shipment*. Give the participant the instructions and materials to collect a first-void urine sample to bring back to SV2 if not completed at SV1.

4.2.4.9. CT Informed Consent (Required)

a) Description of CTs

Provide women interested in HRT, DM, or both components a detailed in-depth description of the CTs before signing the consent. Provide an information-sharing session with a CC staff person who is trained and certified for this task. You can supplement this process with the previously-developed DM and/or HRT videos, however, these old videos *do not* replace the required WHI Consent video. If either of the old videos are used as a supplement, provide the participant with the appropriate handouts that identify inaccuracies in the videos (see *Vol. 2 - Appendix F, Figures F1.2 - F1.4*). For CCs not showing the old DM/HRT videos, the front part of the handout is still an appropriate and helpful supplement, although it is not required. For efficiency, the description of the CT may be done in groups of 8-10 women. During your descriptions, stress that you are especially interested in women who will join both the HRT and DM components. Suggested scripts you might follow are included in *Figure 4.12 - HRT Consent Script* and *Figure 4.13 - DM Consent Script*. If you do not follow the scripts, you must cover the following points during the informed consent discussion:

General CT

- The study is completely voluntary and the participant may withdraw at any time. However, if she drops out, no one can take her place.
- Any information she gives us will be held completely confidential and will be released to no one except WHI personnel and, if necessary, authorized FDA (HRT only) staff.
- Her responses will be added to those of other women and only composite or grouped information will be released. Neither her name nor any other identifying information will be released in WHI reports or publications.
- The assignment to treatment groups is completely random, a computer makes the selection, and both groups are equally important.
- The participant should be willing to take part in either group for DM (Comparison or Dietary Change) or HRT (active or placebo).
- Provide a full description of the CT components remaining screening procedures, follow-up procedures, schedules, and possible adverse effects (see component-specific key points listed below).

HRT Intervention (HRT)

- **Remaining Screening Procedures**: The participant will have several other procedures during the rest of the screening process. These will include:

  Mammogram: Women will be asked to obtain a low-dose x-ray of their breast (known as mammogram) or forward a recent mammogram report

  ECG or electrocardiogram: Wired will be placed on her chest, while she is lying down, to record her heart's activity. There should be no risk of associated with this activity.

  Clinical Breast Exam: A WHI Clinician will examine her breasts and teach her how to examine your own breasts.

  Pelvic exam and Pap smear: A WHI clinician will perform a Pelvic exam and Pap smear. This is the same type of procedure that is done at a doctor's office.

  Endometrial Aspiration: A specially-trained WHI clinician will perform a test of the lining of her uterus. You may feel some cramping after the test, which can be treated with medicine.

  Grip strength: "Some women ages 65 or over will be asked to squeeze a hand-grip tool to measure your grip strength. There is no risk to this procedure."

Six-meter walk: "Some women ages 65 or over will be timed while walking about 18 feet. There is no risk to this test, but you may be tired for a few minutes after you're done."

Chair stand: "Some women ages 65 or over will be asked to stand up from a chair rapidly for 15 seconds. There is no risk to this test, but you may be tired for a few minutes after you're done."

Cognitive assessment: "Women ages 65 or over in the HRT program will be asked to do an interview on concentration and memory. There is no risk to this procedure."

- **Study Pills:** The participant will be asked to take a pill every day. If she has a uterus, it will either contain two hormones or no hormone medicines (placebo); if she does not have a uterus, it will either contain one hormone or no hormone medicines (placebo).

- **Follow-up Visits:** The participant will be asked to come into the CC once a year to repeat measurements and lab procedures similar to the screening tests she has already had (height, weight, waist and hip circumference, blood pressure and blood draws). She will also be asked to complete a *Form 33 - Medical History Update* at semi-annual contacts (via mail, phone, or visit at CC discretion). Some of the tests will only be performed at certain annual visits. Some participants may have additional tests performed. If she has a uterus, the participant will be monitored with a yearly pelvic exam (similar to the screening exam she has at the beginning of the study) and she will have a Pap smear every three years. In addition, she will be interviewed every six months to discuss any symptoms or health events and to get a new bottle of pills.

- **Self-monitoring:** For the first year the participant with a uterus will be asked to record any spotting or bleeding she might have on *Form 53 - HRT Calendar*.

- **Risks:** There is a risk that the participant may have short-term side effects from study pills like breast tenderness or headaches. There is a small risk of more serious problems from the hormones such as cancer, blood clots in your lungs or legs, or gallstones (review with the participant the risks and benefits table on the HRT consent). There is also a very small risk of infection or puncture from the biopsy of the lining of her uterus. There is a small risk associated with drawing the participant's blood (possibility of bruising or infection at the site of the blood draw). However, the health care professionals here are very concerned about her safety and will be very careful with these procedures in addition to the regular monitoring. A mammogram uses radiation, which may slightly increase the risk of developing breast cancer. It is believed by scientists of the WHI and the National Cancer Institute that this small risk is outweighed by the benefit of finding breast cancer early.

Dietary Modification Trial (DM)

- **Remaining screening procedures:** The participant will have several other procedures during the rest of the screening process. These will include:

  ECG or electrocardiogram: Wired will be placed on her chest, while she's lying down, to record her heart's activity. There should be no risk of associated with this activity.

  Mammogram: Women will be asked to obtain a low-dose x-ray of their breast (known as mammogram) or forward a recent mammogram report

  Clinical Breast Exam: A WHI Clinician will examine her breasts and teach her how to examine your own breasts.

- **Follow-up visits:** The participant will be asked to come into the CC once a year to repeat measurements and lab procedures similar to the screening tests she has already had (height, weight, waist and hip circumference, blood pressure and blood draws). In addition, she may be asked to keep careful records of the foods she eats and how they are prepared on to answer the questions during a telephone interview or to answer the questions during a telephone interview. She will also be asked to complete a *Form 33 - Medical History Update* at semi-annual contacts (via mail, phone, or visit at CC discretion).

- **Risk:** There are no known risks associated with making the dietary changes. There is a small risk associated with drawing the participant's blood (possibility of bruising or infection at the site of the blood draw). However, the health care professionals here are very concerned about her safety and will be very careful with these procedures. A mammogram uses radiation, which may slightly increase the risk of developing breast cancer. It is believed by the scientists of WHI and the National Cancer Institute that this small risk is outweighed by the benefit of finding breast cancer early.

Dietary Change Group

- **Group meetings:** Participants in the Dietary Change group will attend group meetings led by a nutritionist to learn how to make dietary changes (reduce fat and increase servings of fruits, vegetables and grains).
- **Schedule:** During the first year, group meetings are once a week for six weeks, every two weeks for six weeks, and once a month for the next nine months. Group meetings last about two hours. There is one individual meeting with a nutritionist during the first year. Starting in the second year and until the end of the study, there will be four group meetings per year to help the participant maintain her eating pattern changes.
- **Make-ups:** If the participant cannot come to a group session, she will be asked to make it up.
- **Self-monitoring:** The participant will be asked to keep careful records of the food she eats as she makes changes.

Comparison Group

- The participant will not be asked to change the way she usually eats.

b) Review of CT Consent Forms

Give the participant the consent form(s) for the CT components she is interested in and eligible for. Instruct her to bring the form(s) home and to read carefully before SV2. Tell her to bring the form(s) with her to the SV2, at which time she will be asked to sign the form(s) after she has had all of her questions answered.

c) Signing of CT Consent Forms

The CCs have the option to review the CT consent forms at either SV1 or SV2 (although the SV2 is recommended to allow sufficient time to review and consider the consent). The CT consent forms will be signed and witnessed after the CC reviews the content of the consent forms with the participant. The appropriate WHI signer should be determined by the CC PI and approved by the local IRB (some IRBs require a specific signer and/or witness and some do not). Give the participant one copy of the consent form and place the other copy in the participant's file. If the participant declines to sign the CT consent forms and is not interested in the OS, do no further screening activities and thank the participant for her time. Baseline forms need not be processed. However, *Form 11 - Consent Status* should be completed and data entered.

4.2.4.10. Hormone Interview (Required)

All CT and OS participants will be interviewed regarding their past use of hormones. If a participant has used hormone preparations in the past, the interview will take approximately 10 minutes to complete. See *Form 43 - Hormone Use* form instructions in *Vol. 3 - Forms* for a detailed description of this interview procedure.

4.2.4.11. Distribute Forms to CT Participants (Recommended)

Give the participant *Form 30 - Medical History Questionnaire* and *Form 31 - Reproductive History Questionnaire* to complete at home and bring back with her to SV2. Alternatively, she may complete these

forms at any time during the screening process, but they must be completed before randomization or enrollment.

4.2.5. Observational Study Participants

Women who choose not to participate in or are found to be ineligible for the CT will be invited to participate in the OS. Complete the remaining baseline activities for the OS and enroll the participant in the OS at this time. See *Section 8 - Observational Study* for a more complete description of activities specific to the OS.

4.2.5.1. OS Informed Consent (Required)

a) Description of the OS

The participant will be informed generally about the OS at the beginning of SV1. Describe the purpose and procedures of the OS to the participant. If she is not eligible for or interested in the CT, inform the participant that she is eligible for the OS and arrange an information-sharing session with a CC staff person who has been trained and certified for this function. A suggested script you might follow is shown in *Figure 4.14 - OS Consent Script*.

Even if the script is not followed, you must cover the following points in this session:

- The study is completely voluntary and the participant may withdraw at any time.
- Any information she gives will be kept completely confidential and will be released to no one except WHI personnel.
- The participant's responses will be added to those of other women and only composite or grouped information will be released. Neither her name nor any other identifying information will be released in WHI reports or publications.
- Provide a full description of the OS component and possible adverse effects.

b) Review of OS Consent Form (Required)

Give the participant a copy of the *OS Consent* to read. Review the consent form with her and answer any questions she may have.

c) Signing the OS Consent Form (Required)

Ask the participant to sign and date two copies of the consent form in the appropriate places. Sign one or two copies of the form yourself as required by your CC's IRB, as a WHI representative and witness, and date the form. Give one copy of the consent form for the participant to take home with her. See *Section 8.2.4 - Entry Into OS Outside a CC Visit* for information on OS consent by mail. If the participant declines to sign the OS Consent, do no further screening activities and thank her for her time.

4.2.5.2. Distribute Questionnaires to Observational Study Participant (Required)

When a participant is enrolled in the OS, give her the baseline CT and OS questionnaires to complete. It is recommended that participants fill out these questionnaires at the CC to assure that these baseline data are obtained. Alternatively, the participant may complete these forms at home. Note that participants will not be enrolled in the OS until their questionnaires have been received by the CC. See *Section 8 - Observational Study* for a list of forms to give to OS participants.

If the participant will complete the forms at home, give her a mailer with prepaid postage in which to mail the forms back to the CC.

4.2.5.3. Completing SV1 for OS Participants (Required)

Explain to the participant that she will receive a *WHI Matters* newsletter in six months and then yearly at the same time. Each year she will also receive questionnaires to complete and mail back to the CC. These questionnaires ask about medical problems or other events that may have occurred during the year. Inform her that she will be contacted again in three years and invited to return for a 3-year follow-up visit to the CC.

4.2.5.4. OS Enrollment (Required)

See *Section 8 - Observational Study* for a list of activities that must be completed before enrolling a woman in the OS. When all of the required activities are completed, enter the information into the database and enact the database function to enroll the participant (see *Section 4.6 - Randomization and Enrollment*).

4.2.6. Exit Interview

Review the SV1 checklist to be sure you completed (or tried to complete) all of the tasks at the visit.

Review any abnormal test results with the participant and arrange for appropriate referrals.

Inform the participant of what to expect during SV2.

Instruct the participant to contact the CC at any time she has questions or concerns.

If the participant is not interested in participating in the CT or OS, complete *Form 11 - Consent Status*. If the participant indicates she may be interested at a later date, record the re-contact date on the form and follow the CC's procedure for entering the participant's information in a "future tickler" file.

After completing the procedures and forms, spend a few minutes talking with the participant about her experience and future involvement in WHI. This helps the participant to establish rapport with the CC staff and develop a sense of commitment to the study. The appropriate means for building rapport depends on the participant. Be sensitive to the best way to bond with each individual participant.

For future contacts, it may be helpful to write informal contact notes in the participant's file about the participant's concerns, interests, questions, significant experiences, or style of interaction, and any information that may need to be reviewed as staff assessment items before randomization.

4.2.6.1. Schedule an Appointment for SV2

Schedule an appointment for SV2. Clinical Centers may have different appointment-scheduling systems depending on their size and resources. Complete an appointment card and give it to the participant. (See model in *Figure E.3.2 - Model Appointment Card*.)

Schedule SV2 for a date that is one to three weeks after SV1 (unless she needs to do a hormone washout for HRT). Remind the participant that she will be asked to return to the CC every year, as close as possible to the same date as SV3. Select a date that will be convenient for the woman's usual yearly plans. For example, if she routinely takes a vacation in July, do not schedule SV2 so that SV3 will fall in that month.

Schedule an appointment for a bone densitometry if your CC is one of the designated bone densitometry CCs.

4.2.6.2. Participant Hand-Outs (Required)

Make sure the participant leaves with all the materials you handed out, including:

- Copy of *Initial Consent* (Required)

- Copies of appropriate DM and/or HRT Consent(s) to read at home and sign at SV2 or *OS Consent* to mail in to CC. (Recommended)
- Questionnaires to complete at home (recommended): *Form 30 - Medical History Questionnaire* and *Form 31 - Reproductive History Questionnaire* for CT participants (unless these forms were completed in the CC) or remaining baseline questionnaires for OS participants with manila envelope and prepaid postage or mailing label.

4.2.7. Post-Visit Review

The post-visit review includes an evaluation of lab results and a determination of eligibility after the CT participant leaves the SV1 but before she returns for SV2.

4.2.7.1. Blood Analysis Results (Required)

The following are general WHI guidelines. Check your CC-specific guidelines for alert values for blood test results.

Review the complete blood count (CBC) results when they return from the local laboratory. Participants with a hematocrit < 32%, or platelet count < 75,000 cells/ml are at least temporarily ineligible for the study. If the participant is temporarily ineligible, you can repeat the blood draw and analysis when you or the participant suspect the values have increased sufficiently above the criterion levels. See *Section 4.5.4.4 - Ineligible at SV1 or Later Screening Visits* for other criteria that make a participant temporarily ineligible and may be rescreened at a later date. The participant's information or folder should be entered in a "future tickler" file using your CC's established procedure, if you intend to rescreen CBC results

If a triglyceride level was done because of lipemic sera, a level $\geq$ 500 mg/dl will exclude a woman from the HRT and require a referral to her primary physician for further evaluation.

To review blood results:

- Log in the receipt of the blood results from the local lab (each CC should devise this system for its own use).
- Attach the results to *Form 100 - Blood Collection and Processing*.
- Review the blood results for eligibility.
- Enter the results in the database.
- Place the results in the participant's file.

If the participant is ineligible for the CT based on blood results, contact the participant and inform her that she needs to see her primary physician to investigate an abnormal blood value. Invite her to call the CC after the lab results are fully investigated and her doctor says it is okay for her to participate in the study, at which time she may have another blood sample drawn. You may call her physician to report the blood abnormality and fax a copy of the blood report to him/her.

4.2.7.2. Scanning and Key-Entry of Data from SV1

Data enter (scan or key-enter) all forms for participants who continue to be interested in and eligible for the CT or OS as soon as possible and run an Eligibility Determination (Tasks 910, 920, 940, as appropriate) in WHILMA. For participants who are ineligible for or not interested in CT or OS, *Form 2/3* and other screening data to which the participant has consented should be entered as soon as possible so that eligibility information can be tracked in the database.

4.3. SV2

The recommended and required procedures for SV2 should minimize the participant's time burden and assure that baseline CT measurements and eligibility are determined appropriately. Activities in SV2 will vary depending on a participant's interest in and eligibility for the HRT, DM or both.

Each CC can organize the flow of SV2 to fit its needs as long as the flow meets the following requirements: (Once established, the flow within each CC should be consistent for all SV2s conducted at that CC.)

- Outline again the CT objectives and expectations, and answer any questions the participant may have.
- Obtain a signed HRT, DM, or OS Consent before collecting any more information or performing any other procedure.
- Limit the time required of the participant at SV2 to approximately three to four hours. Women interested in both HRT and DM may have a longer SV2 because they will have procedures and teaching for both CT components.

It is recommended that the participant should not wait more than 10 minutes past her appointment time to be seen by CC staff.

4.3.1. Purpose of SV2

The purpose of SV2 is to:

- Continue to build rapport with the participant and promote her interest in the study.
- Confirm continuing eligibility by reviewing SV1 lab and other measurement results.
- Perform additional clinical procedures to determine eligibility.
- Dispense HRT enrollment pills and instruct participants with a uterus on how to record bleeding on *Form 53 - HRT Calendar* (HRT).
- Instruct the participant in the completion of *Form 62 - Four-Day Food Record (4DFR)* (DM).

The SV2 is the first CC visit in which DM and HRT participants experience the more sensitive and invasive procedures of the study (ECG and clinical breast exam for participants in both components; pelvic exam and Pap smear for HRT participants, and endometrial aspiration for HRT participants with a uterus). Each participant should be reassured that these procedures are performed to ensure her safety in the CT. Each CC staff member must continue to show a professional and caring manner and show the continued gratitude of the WHI staff for her ongoing commitment to the study. As with SV1, the staff need to be available to answer any questions the participant may have about the trial and be fresh and enthusiastic.

4.3.2. Activities During SV2

A suggested scenario for SV2 is described below. Flexibility in the scenario is identified in parentheses.

- Review the HRT and/or DM Consents with the participant. Obtain signed consent, as appropriate, and provide a copy to the participant before other SV2 procedures are done.
- Perform a fasting blood draw (if not done at SV1).
- Review Complete Blood Count (CBC) results (if drawn at SV1).
- Review *Form 30 - Medical History Questionnaire* and *Form 31 - Reproductive History Questionnaire* if previously given to the participant (may be done at SV3).
- Perform a 12-lead electrocardiogram (ECG) (may be done at SV3).
- Perform a clinical breast exam (CBE) (may be done at SV3).

- Teach breast self-examination (BSE) to the participant (may be done at SV3).
- Perform a pelvic exam and Pap smear (HRT). (See *Section 4.3.4.4.f - SV2* Procedures, *Pelvic Exam and Pap Smear* for exceptions.)
- Perform an endometrial aspiration (for HRT participants with a uterus). (See *Section 4.3.4.4.g - SV2* Procedures, *Endometrial Aspiration* for exceptions.)
- Dispense enrollment pills (HRT).
- Instruct the participant on how to record information (e.g., bleeding) on *Form 53 - HRT Calendar* (HRT participants with a uterus).
- Review the *HRT Handbook* with the participant.
- Instruct the participant how to complete the *4DFR* (DM).
- Schedule a mammogram or request results if the participant had a mammogram within the past 12 months.
- Give the participant *Form 32 - Family History Questionnaire*, *Form 34 - Personal Habits Questionnaire*, and *Form 37 - Thoughts and Feelings* to complete at home or in the CC.
- Schedule SV3.

If a participant volunteers any change in the information she previously provided on *Form 2/3 - Eligibility Screen* regarding her health or circumstances that now make her ineligible (e.g., subsequent heart attack, cancer diagnosis, intention to move away from the area, recent vaginal bleeding, hysterectomy, etc.), update her *Form 2/3 - Eligibility Screen* responses.

Enroll in OS if the participant is not interested in or eligible for DM or HRT.

4.3.3. Preparation for SV2

Participants interested in the CT components should have had their SV2 scheduled at the end of SV1. Preparation for the SV2 follows a schedule similar to that for the SV1.

4.3.3.1. Two Weeks Before SV2

Two weeks before SV2:

- Phone or mail a reminder card to the participant with the date and time of her SV2 and a number to call if she has any questions. If the participant did not have a SV1 blood draw, add a reminder not to exercise vigorously or eat or drink anything (except water) during the 12 hours before the CC visit. She should take her regular medications, with the exception of insulin for participants who have diabetes. Diabetic participants can be instructed to bring their insulin with them to take after the blood draw or as their physician advises.

- Run an eligibility determination in WHILMA (Task 910, 920, or 940, as appropriate) to confirm that she is still eligible for the component(s) in which she is interested. (See *Vol. 5 - Data System, Section 6.1 - Eligibility Determination.)*

4.3.3.2. One Week Before SV2

Each week, prepare for SV2 participants scheduled for the next week.

- Review the file of each participant scheduled for an SV2. The participant file should contain all general CT and component-specific forms used during the SV2, appropriate CT instructional materials, SV2 checklist, and enough participant barcode labels for the visit forms, any specimens such as Pap smears, and study pill bottle labels for HRT enrollment pills.

- Review the SV1 activities to see if the participant had a fasting blood draw at SV1. If she did not, put a *Form 100 - Blood Collection and Processing* in the SV2 file and indicate on the SV2 checklist that a blood draw is needed. If a blood draw was completed at SV1, check that the local lab results of the CBC are available. If the results are available, review each result for alerts (see *Section 4.3.4.4.b - SV2* Procedures, *Review Complete Blood Count*). If the CBC results have not been received from the local lab, call the lab for the results. (You may use the results of the CBC you receive by phone report, but indicate on *Form 100 - Blood Collection and Processing* that the results were obtained over the phone and verify them when the paper copy arrives from the local lab.)

An additional phone call reminder to participants may be made 1 to 3 days before the SV2.

4.3.3.3. Activities on the Morning of SV2

Each day prepare for the SV2s scheduled for that day. See *Section 9 - Clinical Measurements* for further details on the procedures and related equipment for the SV2 clinical measurements (e.g., pelvic exams and Pap smears, endometrial aspirations).

- Stock and prepare trays and blood tubes for any blood samples needed.
- Check that other supplies and equipment needed for the various procedures are available.
- Set up trays for pelvic examinations for the day, each including: plastic disposable or metal specula, disposable gloves, glass slides, Pap fixative spray, wooden spatula, cervical brush, and cotton-tipped swabs.
- Check that the light source for Pap smears and endometrial aspirations is in working order.
- Set up trays for endometrial aspirations for the day, each including: flexible aspirator; syringe, 20-gauge spinal needle, 1% lidocaine (20% benzocaine gel may be used in place of lidocaine injection), and tenaculum (if used at your CC), barcode-labeled formalin bottle; multiple-sized specula (either disposable or metal); dilators or sounds; disposable gloves; and scissors.
- Check that the ECG machine is stocked with ECG paper and alcohol swabs, that all electrodes and cables are in place, and that there is enough memory left for the recording.
- Check participants' files to be sure you have received blood results (see *Section 4.3.3.2 - One Week Before SV2*). If not, call the local lab for the report(s).

4.3.4. Guidelines for SV2 Activities

Figure 4.5 - Overview of SV2 identifies the recommended scenario for screening tasks that can be completed at SV2. Use a screening visit checklist (see *Figure E.4.3 - Model SV2 Checklist*) as a guide for completing all of the tasks at SV2. Check each activity and form and indicate if you did or did not complete the task.

4.3.4.1. Reception

See *Section 4.2.4.1 - Reception* for guidelines. Spouses or other support persons should not accompany the participant into the examination rooms.

4.3.4.2. Clinical Trials Consent Form (Required)

A participant must sign the appropriate CT consent(s) before you perform any clinical trial-specific activities. The participant will have had at the SV1 instruction regarding the CT and the opportunity to watch the WHI Consent video. The participant will also have taken home from SV1 a copy of the CT consent form(s) for the trial components in which she is interested.

At the beginning of SV2, give the participant time alone with the designated staff member who reviews informed consent with participants. If a thorough informed consent discussion did not occur at the end of the SV1, provide appropriate information at this time (see *Section 4.2.4.9 - CT Informed Consent*). Adequate time

should be spent answering any questions the participant may have. The participant will then sign the appropriate consent form for the trial component(s) (HRT or DM) in which she is interested.

If the woman declines to participate in the CT, she may be enrolled in the OS after she is fully informed about the OS and signs the *OS Consent*. *Form 42 - OS Questionnaire* as well as the other baseline forms need to be completed (preferably at the CC or optionally at home) and mailed back to the CC (see *Section 8 - Observational Study*).

Complete *Form 11 - Consent Status*, indicating which consent forms the participant signed or refused to sign along with reasons she refused to sign, if appropriate.

4.3.4.3. Review of Questionnaires (Required)

CT participants may have taken questionnaires home from SV1 to complete and bring back to SV2. Review the forms for completeness. Ask the participant to complete any forms that are grossly incomplete (she may decline to answer questions, however). If the participant reports a change in her health that now makes her ineligible, update *Form 2/3 - Eligibility Screen* (see instructions in *Vol. 3 - Forms, Part C - Reviewing and Updating Form 2/3*).

4.3.4.4. SV2 Procedures

a) ECG (Required)

All women interested in the CT must have a resting 12-lead ECG before randomization at SV3. See *Section 13 - ECG Procedures* for complete instructions. If the ECG MACPC readout indicates an alert condition, notify the CC physician and your supervisor immediately. Weekly, your CC physician should review ECGs done that week and decide on any actions based on that review.

b) Review Complete Blood Count (Required)

Obtain the local lab results for the CBC drawn at SV1 (or SV2, depending on your CC's screening scenario). Take the actions listed below for particular lab values:

Test	Abnormal Cut-Off	Action
White blood cell count	< 1,000 cells/ml	Urgent referral to primary physician.
Hematocrit	< 30% < 32%	Urgent referral to primary physician. Exclude temporarily.
Platelet count	< 50,000 cells/ml < 75,000 cells/ml	Urgent referral to primary physician. Exclude temporarily.

"Urgent referral" requires notification of the participant before she leaves the CC or immediately upon receipt of the finding from the laboratory and notification of the participant's primary physician within the week. The PI and your CC physician may have defined other alert values and actions for laboratory results. Refer to your CC guidelines or check with your Clinic Practitioner. Verify alerts with printed results when they are available from the local lab.

c) Clinical Breast Exam (CBE) (Required)

Perform a CBE on CT participants at SV2 (SV3 at the latest) and complete *Form 84 - Clinical Breast Exam*. See *Section 9.7.2 - Performing the Clinical Breast Exam* for a complete description of this procedure. Any breast abnormality findings temporarily exclude the participant from the CT. If you observe any abnormal findings, refer the participant to her primary physician. Instruct her that once her

primary physician has fully investigated the findings and found them to be benign, she should contact the CC again if she is still interested in participating in the study.

d) Breast Self-Exam (BSE) (Required)

Teach the participant to do BSE at SV2. See *Section 9.8.2 - Performing Breast Self-Exam (BSE) Instruction* for a full description of this procedure and complete the corresponding question on *Form 84 - Clinical Breast Exam*.

e) Mammogram (Required)

Schedule the mammogram or write or call for mammogram results if the participant has had a mammogram in the past 12 months. WHILMA compares the date to the last mammogram listed on *Question 5, Form 85 - Mammogram* to the contact date indicated on *Form 85 - Mammogram* to determine the 12 month window. The results must show that the participant is free from findings suspicious of cancer before randomization. Refer to *Section 12 - Mammogram* for more details. A mammogram done in the 12 months before SV2 is acceptable as a baseline mammogram. Check the participant's *Form 20 - Personal Information* for the date of her last mammogram. If the woman has not had a mammogram in the past 12 months:

- Schedule a mammogram appointment for her if your CC has an agreement with a mammographic facility to provide study mammograms.
- If she prefers to have a mammogram arranged through her primary physician, ask her to call her doctor to have one scheduled. Ask her either to 1) request the facility to forward the results directly to the CC, or 2) call the CC with the date of her mammogram and name of the mammographic facility so that you can request the results.

If the participant had a mammogram within the past 12 months:

- Check *Form 20 - Personal Information* to be sure the name and address of the mammographic facility is available. Verify the address with the participant. If the participant does not know the name of the facility, you could contact the physician who referred her for a mammogram to obtain a copy of the mammogram report.
- Write or call the mammographic facility or the participant's physician for a copy of the participant's mammogram result.
- Send the mammographic facility or the participant's physician a copy of the participant's *General Medical Release Form*.
- Fill in the appropriate items on *Form 85 - Mammogram*.

The mammogram report may be mailed or faxed to the CC and attached to *Form 85 - Mammogram*. If the staff at the mammographic facility insist that they can only read the report, have your Clinic Practitioner take down the report verbatim over the phone, date and initial the report, and document who read the report over the phone. These notes should then be attached to *Form 85 - Mammogram*.

f) Pelvic Exam and Pap Smear (HRT) (Required)

Perform a pelvic exam and Pap smear on all potential HRT participants. Summarize the pelvic exam results and fill in the appropriate items regarding the Pap smear on *Form 81 - Pelvic Exam* and *Form 92 - Pap Smear*, respectively. If the participant has had a Pap smear within the past 12 months and the cytology results can be obtained, only a pelvic exam needs to be done. Women with and without a uterus should have a pelvic exam and Pap smear. See *Section 9.9.2 - Performing Pelvic Exam and Obtaining the Pap Smear* for a description of this procedure.) See *Section 5.1.2.3 - Exclusions Based on Baseline Pap Smear, Section 5.1.2.2 - Exclusions Based on Baseline Pelvic Exam Findings,* and *Section 4.3.6.3 - Pap Smear Results (HRT)* for details on exclusions from HRT based on Pap smear and pelvic exam results.

If a previous Pap smear is to be accepted as baseline, arrange to receive a copy of the cytology report. (See procedures for requesting mammogram reports in *Part e* above.)

g) Endometrial Aspiration (HRT) (Required)

Review the *HRT Handbook* section about the endometrial aspiration with the participant before the procedure.

Perform an endometrial aspiration on all potential HRT participants with a uterus and complete the initial part of *Form 82 - Endometrial Aspiration*. If the participant refuses to have or complete an endometrial aspiration, she is not eligible for the HRT. If she agrees to the procedure at a later date, she can then be considered for HRT eligibility at that time. If the participant has had an endometrial aspiration or a diagnostic D&C within the past 12 months, an endometrial aspiration will not be necessary at baseline, provided that the pathology results are obtained. (See procedures for requesting mammogram reports in *Part e* above.)

Record the appropriate information on *Form 82 - Endometrial Aspiration*. A previous transvaginal ultrasound report will not be accepted as a baseline exam.

If you are unable to perform the aspiration because of cervical stenosis, even after using a paracervical block, a second attempt should be made by the CC Consulting Gynecologist. If you are still not able to perform the aspiration, schedule a transvaginal ultrasound of the uterus. If the consulting Gynecologist judges the Clinic Practitioner's skill to be exemplary such that the gynecologist would not be able to perform an endometrial aspiration on a second attempt either, the second attempt may be bypassed. (See *Section 4.3.6.5.h - Transvaginal Uterine Ultrasound* below.)

See *Section 5.1.2.4 - Baseline Endometrial Evaluation* and *Section 5.1.2.5 - Exclusions Based on Baseline Endometrial Evaluation* for interpretation of endometrial aspiration results based on HRT exclusion criteria.

h) Transvaginal Uterine Ultrasound (HRT) (As Needed)

Schedule a transvaginal uterine ultrasound for potential HRT participants with a uterus who are unable to have an endometrial aspiration because of cervical stenosis. If the transvaginal ultrasound cannot be performed or if an accurate reading cannot be done, the woman is ineligible for HRT. Note that a transvaginal uterine ultrasound performed in the past 12 months is not acceptable as a baseline exam. See *Section 5.1.2.6 - Exclusions Based on Transvaginal Uterine Ultrasound* for details on exclusion criteria for HRT based on ultrasound results.

i) Dispense Enrollment (Run-In) HRT Pills (HRT) (Required)

Dispense an HRT enrollment bottle to interested women at SV2. The participants must have signed the HRT Consent before you dispense the enrollment pills. A participant can only have two enrollment trials and still be eligible for HRT. See *Section 15.4.1 - Selecting and Dispensing HRT Bottles at SV2*.

- Inform the participant that you will give her study pills to start taking. She should start taking the pills the day of SV2. Do not tell her that these are placebo pills. A suggested script you might follow is shown in *Figure 4.15 - Suggested Script for Blinded Study Medication Dispensation*.
- Ask the participant if she wants a non-child resistant cap for her study pill bottle and obtain appropriate signatures (see *Section 15.1.3 - Child Resistant Caps*).
- Review each item of the *HRT Study Pills Instructions* in the *HRT Handbook* and give her a copy of the *Handbook.*
- Offer her a WHI pill organizer. She should bring her organizer (if used) along with her WHI pill bottles, including any remaining study pills, to each CC visit.

- Instruct her to keep the study pills in a safe place in her home out of the reach of children or animals.

j) Provide *Form 53 - HRT Calendar* Instruction (HRT) (Required)

- Give each HRT participant with a uterus a copy of *Form 53 - HRT Calendar* with her study pills.
- Stress to the participant that completing this form should be a daily activity and should not be done after the fact. She will record in the *HRT Calendar* whether any bleeding occurred that day and estimate the amount of bleeding that she had.
- Explain how to fill in the ovals and advise the participant that any comments she would like to add can be written on the last page. See *Vol. 3 - Forms, Form 53 - HRT Calendar* for further instructions.
- Ask the participant to return the *HRT Calendar* at her next visit. Also encourage her to call the CC if she has any questions.

k) 4DFR Instruction (Required)

At SV2, have all DM and HRT+DM participants watch the *4DFR* videotape and provide them with *Form 69 - Keeping Track of What You Eat*. Provide the participant with the *4DFR* (*Form 62)* and record in the booklet the specific days to record. Provide the participant with the name of a Dietary Assessment staff person to call with questions. A Dietary Assessment staff person should be available to answer questions at the end of the video. Refer to *Section 10.1.1 - Dietary Assessment Activities at SV2* for detailed procedures.

4.3.4.5. Observational Study Participants

Women at SV2 who are not interested in or eligible for the CT will be invited to enroll in the OS. Complete the OS informed consent process and the remaining baseline forms (including *Form 42 - OS Questionnaire*). Preferably, participants will complete these forms at the CC, but may be allowed to take them home and mail them back to the CC. OS participants will not be enrolled until all of the baseline forms are completed. (See *Section 8 - Observational Study* for more details.)

4.3.5. Exit Interview

Review the SV2 checklist to be sure you completed all the necessary tasks during the visit.

If the participant is not interested in or eligible for the CT or OS, complete *Form 11 - Consent Status* indicating she has declined further screening. If she indicates she may be interested at a later date, record the re-contact date on that form and follow your CC's procedure for entering the participant's information in a "future tickler" file.

After completing the SV2 procedures and forms, spend a few minutes talking with the participant. This helps to establish rapport and create a commitment to the study. The appropriate means for building rapport depends on the participant. Be sensitive to the best way to bond individually with each woman.

For future contacts, it may be helpful to write informal contact notes in the participant's file about her concerns, interests, questions, or style of interacting and any information that may need to be reviewed as staff assessment items before randomization.

Inform the participant of what to expect at SV3 (see *Section 4.4.4 - Activities During SV3*).

Instruct the participant to contact the CC any time she has questions or concerns.

4.3.5.1. Schedule an Appointment for the Third Screening Visit

Schedule an appointment for SV3 for CT participants. Each CC will have a different appointment-scheduling system depending on its size and available resources. Complete an appointment card and give it to the individual.

Schedule SV3 allowing sufficient time to obtain mammogram and pathology results. If the mammogram results are available by SV2, DM-only women could potentially return in as few as 8 days after they have completed *Form 62 - 4DFR*. HRT women, however, require 28 days before the SV3 to allow time to complete the enrollment period. If SV3 occurs more than six months after SV1, the baseline measurements and questionnaires will need to be repeated. (See *Section 4.5.3 - Time Limits During Screening*.)

4.3.5.2. Participant Hand-Outs

Make sure the participant leaves with all the materials you have handed out, including:

- *Form 62 - 4DFR* with dates for recording written on the front, and *Form 69 - Keeping Track of What You Eat* (DM) (Required)
- *Form 32 - Family History Questionnaire*, *Form 34 - Personal Habits Questionnaire*, and *Form 37 - Thoughts and Feelings* (recommended for completion at home or at beginning of SV3)
- One bottle of HRT enrollment pills (HRT) (Required)
- *Form 53 - HRT Calendar* (HRT) (Required for participants with a uterus)
- *HRT Handbook* (HRT) (Required)
- Appointment card, indicating SV3 appointment (Recommended)
- Appointment for mammogram (if mammogram not done in the past 12 months) (Recommended)

4.3.6. Post-Visit Review

The post-visit review includes an evaluation of lab results and a determination of eligibility after the participant leaves the SV2 but before she returns for SV3.

4.3.6.1. Blood Analysis Results (Required)

Review the blood results when returned by the local laboratory if blood was drawn at SV2. Follow procedures in *Section 4.2.7.1 - Blood Analysis Results* .

4.3.6.2. Mammogram Results (Required)

Review the radiologic report of the participant's baseline mammogram. Summarize the results on *Form 85 - Mammogram*. Results suspicious or highly suggestive of malignancy will, at least temporarily, exclude the participant from the study.

A probable benign finding recommending short interval follow-up will not exclude the participant from the study. Note in a "future tickler" file when the participant should have a repeat mammogram.

The primary physician must be notified and sent a copy of abnormal mammogram reports. The participant should be told of the findings by a CC physician or Clinic Practitioner and instructed to make an appointment with her primary physician for further management. Inform the participant that if the work-up shows the problem to be benign, she should call the CC if she is still interested in participating in the study.

If the participant approves, normal mammogram reports can be copied and given to her or sent to her primary physician. See *Section 12.4 - Actions Based on Mammogram Reports* for more details on review of mammogram results.

4.3.6.3. Pap Smear Results (HRT) (Required)

Review results of the Pap smear report when it comes back from the cytology lab and summarize the results on *Form 92 - Pap Smear.* See *Vol. 3 - Forms* for more details. Invasive cervical cancer will exclude the participant from the HRT.

Moderate to severe dysplasia of the cervix results in a temporary exclusion. Refer her to her primary physician for work-up. See *Section 5.1.2.3 - Exclusions Based on Baseline Pap Smear*. Use similar procedures for referral of abnormal results as for mammograms (see *Section 4.3.6.2 - Mammogram Results*).

4.3.6.4. Endometrial Aspiration (HRT) (Required)

Review the pathology report of the endometrial aspiration. Summarize the report on *Form 82 - Endometrial Aspiration*. Cancer, atypia, and hyperplasia (cystic and adenomatous) will exclude the participant from the HRT. If the report gives any of these diagnoses, use a similar procedure for referral of abnormal results as for mammograms (see *Section 4.3.6.2 - Mammogram Results*).

If the participant approves, reports can be copied and given to her or sent to her primary physician.

Note that baseline endometrial aspirations will not have a central pathological review.

Participants with findings of significant endometrial fluid will be temporarily ineligible. If a follow-up pelvic ultrasound shows no abnormalities, then she can be made eligible.

4.3.6.5. Transvaginal Uterine Ultrasound (HRT) (As Needed)

If a transvaginal uterine ultrasound was done, review the results and complete *Form 83 - Transvaginal Uterine Ultrasound*. Women with an endometrial lining of $\leq$ 5 mm will be eligible. Women with an endometrial thickening of > 5 mm or excessive pelvic fluid will be temporarily ineligible for the trial and must be referred to their primary physician with a copy of the ultrasound report. If the abnormal finding is investigated fully and the participant is found not to have hyperplasia, atypia, or cancer, she will be eligible for randomization. Summarize the results of the follow-up on *Form 83 - Transvaginal Uterine Ultrasound*.

See *Section 5.1.2.6 -Exclusion Based On Baseline Transvaginal Uterine Ultrasound* for instructions regarding readings in women with fibroids. Refer other abnormalities to the primary physician, including:

- Uterine masses
- Adnexal masses
- Other masses arising from non-gynecologic origins
- Any other abnormality noted by the reading radiologist or gynecologist

4.3.6.6. Participants Whose Test Results Indicate Temporary Ineligibility (Required)

If the participant is temporarily ineligible because she is awaiting follow-up evaluation of abnormal pelvic exam, Pap smear, endometrial aspiration, or mammogram:

- Ask her to stop taking HRT enrollment pills, if she is still in the enrollment period.
- Cancel the SV3 and reschedule when normal follow-up results are received. (If ineligible because of abnormal follow-up results, follow procedures below in *Section 4.3.6.7 - Participants Whose Test Results Indicate Ineligibility*)
- Dispense a second HRT enrollment bottle when normal follow-up results are received.

4.3.6.7. Participants Whose Test Results Indicate Ineligibility (Required)

If the participant is ineligible due to the pelvic exam, Pap smear, endometrial aspiration, or mammogram results:

- Invite the participant to come to the CC to complete activities for the OS, if she is interested.
- Ask her to bring her HRT enrollment pills to the CC when she returns to complete OS activities (if interested).
- If the participant is ineligible for the CT and declines to participate in the OS:
  - Cancel SV3.
  - If she is on HRT enrollment pills, ask her to stop taking them and to return the pill organizer and study pill bottle with remaining study pills to the CC.
  - Send her a letter thanking her for her time and efforts.

4.4. SV3

SV3 is the final screening visit for the CT participants. Participants who remain eligible for and interested in HRT and/or DM will be randomized accordingly. Participants eligible for and interested in both HRT and DM must be randomized the same day.

Each WHI CC can organize the flow of SV3 to fit its needs. Once established, keep the flow within each CC consistent for all SV3s conducted at that CC.

It is recommended that the participant should not wait more than 10 minutes past her appointment time to be seen by CC staff.

If more than six months have passed between SV1 and SV3, baseline data over six months old must be recollected. See *Section 4.5.3 - Time Limits During Screening* for more details.

4.4.1. Purpose of SV3

The purpose of SV3 is to:

- Continue to build rapport with the participant and promote her continued interest in the study.
- Assure adequate completion of all baseline CT forms.
- Assess HRT enrollment pill adherence (HRT).
- Assess HRT and DM eligibility.
- Randomize participants for HRT and/or DM or enroll in OS.
- Dispense HRT study pills (HRT).
- Assign DM Dietary Change participants to dietary group.
- Complete baseline procedures (subsamples) (e.g., cognitive assessment, functional status, *4DFR* documentation).
- Schedule the next follow-up visit.

The SV3 is the last step in verifying eligibility for the HRT and DM CT components. You will need to check all eligibility data at this visit before randomization.

4.4.2. Activities During SV3

A suggested scenario for SV3 is described below. Flexibility in the scenario is identified in parentheses.

- Review *Form 32 - Family History Questionnaire, Form 34 - Personal Habits Questionnaire,* and *Form 37 - Thoughts and Feelings* for completeness (may be done at earlier visit).
- Obtain, review, and record results of:
    - *Form 62 - 4DFR* (DM)
    - *Form 81 - Pelvic Exam* (HRT) (may be done at earlier visit)
    - *Form 92 - Pap Smear* (HRT) (may be done at earlier visit)
    - *Form 82 - Endometrial Aspiration* (HRT) (may be done at earlier visit)
    - *Form 85 - Mammogram* (may be done at earlier visit)
    - *Form 100 - Blood Collection and Processing* (if not reviewed at SV2)
- Update *Form 2/3 - Eligibility Screen*.

- Update Current Medications.
- Weigh returned HRT enrollment pills (HRT).
- Review *Form 53 - HRT Calendar* (HRT).
- Complete *Form 10 - HRT Management and Safety Interview*.
- Make a final determination of eligibility.
- Randomize participants to HRT and/or DM.
- Dispense appropriate HRT study pills (HRT).
- Assign DM Dietary Change participant to dietary group (DM).
- Document *Form 62 - 4DFR* (DM) (subsample).
- Complete cognitive assessment interview (*Form 39 - Cognitive Assessment*) (subsample).
- Complete functional status measures (*Form 90 - Functional Status*) (subsample).
- Schedule a semi-annual follow-up contact. (*Optional*)
- Enroll in OS if not interested or eligible for DM or HRT.
- Exit interview.

4.4.3. Preparation for SV3 (Required)

The participants interested in CT components should have had an SV3 scheduled at the end of SV2. The SV3 is the last visit to make the final eligibility determination for the CT. Results of all tests and procedures must be reviewed for the final time at this visit.

4.4.3.1. Two Weeks Before SV3

Two weeks before SV3, mail to the participant:

- Reminder card with date and time of SV3.
- Medication bag with WHI logo for participant to use to bring any new medications to SV3, including HRT enrollment pills (and any extra pill organizers).

4.4.3.2. One Week Before SV3

One week before SV3:

- Review the participant's file and determine what procedures and test results must be reviewed. The file should contain all forms to be used in SV3 and an SV3 checklist. All test results should be key-entered into WHILMA before the woman's SV3 so that her final eligibility determination can be made during the visit and randomization will go smoothly.
- Check that the baseline mammogram was done.

  If mammogram results are not yet available, call the mammogram facility and ask that the reports be faxed to the CC. If the report is not yet done, ask to have it faxed as soon as it is available. If it will not be ready for SV3, reschedule SV3. If the participant has not yet had her mammogram, call the participant to reschedule SV3. Ensure that she plans to have the mammogram in the interim and re-confirm the mammogram date.

- Check that the Pap smear and endometrial aspiration biopsy results are available for HRT women:

  Check that the pathology report has been received from the local pathology lab. If the report has not been received, call the lab and ask to have the report faxed to the CC. If the report has not been

prepared, ask to have it faxed to the CC as soon as it is ready. If it will not be ready SV3, it may be necessary for a CC physician or Clinic Practitioner to call the pathologist for a phone report. In such cases, the written pathology report must be obtained later when available and the phone report rechecked.

- Run the eligibility determination for HRT or DM in WHILMA, as appropriate. Follow-up on any problems to assure data are complete by the time of SV3.

The Clinic Practitioner (MD, NP, RN, or PA) must review results of any blood analyses, mammogram, Pap smear, endometrial aspiration, and transvaginal uterine ultrasounds for eligibility and the need for referral of abnormal findings. (See *Section 4.3.6 - Post-Visit Review*.) Abstract these results on the appropriate WHI forms.

4.4.4. Guidelines for SV3 Activities

Figure 4.7 - Overview of SV3 gives the recommended scenario for screening tasks that need to be completed by SV3. Use an SV3 checklist (see *Figure E.4.4 - Model SV3 Checklist* for a sample).

4.4.4.1. Reception

See *Section 4.2.4.1 - Reception* for guidelines.

4.4.4.2. Assess HRT Enrollment Pill Adherence (HRT)

Weigh the HRT enrollment pills returned at SV3 (See *Section 15.6.2.2 - Pill Weighing Procedures*). Enter the weight into the database using the appropriate function. WHILMA calculates adherence for run-in medications when the eligibility determination is run (*Task 920*). WHILMA will calculate adherence based on dates of dispensation, collection, and weight of the remaining pills. If a participant is ineligible due to the HRT enrollment adherence criterion, you can repeat the enrollment one time only but exercise appropriate judgment about whether such a repeat is appropriate. (See *Section 15.4.1.3 - Repeat HRT Enrollment Period* for details.)

4.4.4.3. Review *Form 53 - HRT Calendar*

Any bleeding during this period may exclude the participant from the HRT. Update *Form 2/3* as needed to reflect the recent bleeding. Review bleeding with your Clinic Practitioner and/or consulting gynecologist to determine severity and possible safety concerns. Refer a participant with bleeding to her primary physician for further evaluation if necessary.

4.4.4.4. Complete *Form 10 - HRT Management and Safety Interview*

Complete the *HRT Management and Safety Interview* (*Form 10*) with the participant just as you would for follow-up contacts, following the script on the form. Refer to *Section 16 - Follow-Up* and the form instructions for more details.

4.4.4.5. Review *Form 2/3 - Eligibility Screen*

Review *Form 2/3 - Eligibility Screen* with the woman to verify that she has not experienced any changes in her health or circumstances that would make her ineligible since you last administered the form.

- Use the "Script to Update *Form 2/3*" contained *Vol. 3 - Forms, Form 2/3* Form Instructions, *Part D-Scripts*.
- If the woman answers "Yes" to any of the questions from the update script, update the original *Form 2/3* and key-enter the corrections as described in *Vol. 3 - Forms, Form 2/3* form instructions, *Part C. - Reviewing and Updating Form 2/3.*

4.4.5. Pre-Randomization Discussion

After the participant has completed all activities, procedures, and data collection necessary for determining CT eligibility, sit down with her and review the procedures for the CT components she has consented to join.

4.4.5.1. HRT Eligibility Discussion

At this point participants should be reminded of the requirements for participation (randomizing to possible hormones versus placebo, time commitment, etc.). Review *Form 10 - HRT Management and Safety Interview* to assess adherence information and to discuss symptoms, concerns, or other difficulties that should be addressed before randomization. Complete the appropriate staff and CP assessment items on *Form 6 - Final Eligibility*.

4.4.5.2. DM Eligibility Checklist

At the SV3 before randomization, a certified Lead Nutritionist, Dietary Assessment staff, or Group Nutritionist uses the DM Eligibility Checklist (see *Section 6.1.6 - DM Eligibility Checklist* and *Figure 6.1a* and *6.1b* for details) to assess a participant's ability to complete the activities of the DM Intervention. This review process takes about 30 minutes and requires judgment by the staff who administer this checklist. A participant must provide an acceptable *Form 62 - 4DFR* and pass the DM Eligibility Checklist before she is eligible for DM. The points listed in the DM Eligibility Checklist are the minimum points to cover. They do not need to be covered in any specific order (e.g., the *4DFR* does not need to be reviewed first).

Note: If the Dietary Assessment staff determines that the participant is ineligible for DM at any time during the review, the interview may be ended. Explain to the woman why she is ineligible for DM, thank her for her interest and willingness to take part in the screening process, and explore her interest in joining OS.

4.4.5.3. Questionnaire Review

Review remaining CT forms for missing data and create WHILMA encounters for each form (scan the mark-sense versions).

4.4.5.4. Current Medications Update

A participant will bring to the SV3 any new medications that are prescribed or that she started taking since SV1. Enter any new medications into the database as done at SV1 (see *Section 4.2.4.6 - Current* Medications and Current Supplements Inventory Review) as a new encounter. You only need to enter medications that are "new " to the participant since the SV1 interview. You do not need to re-enter the medications entered at SV1 nor delete any medications that the participant has discontinued since the SV1.

4.4.5.5. Functional Status Measures (Subsample)

Functional status will be measured in a subsample of CT participants ages 65 to 79. Participants in the functional status subsample can be identified by running *WHIP 0527*. Functional status measurements can be done during any screening visit but to eliminate staff burden and it is recommended that you perform the measures at SV2 or SV3 avoid doing measures on participants who may not be eligible for WHI or who enroll in OS. Functional status measures are done on the same subsample of participants at screening and at follow-up visits as outlined in *Vol. 1, Table 1-A1.1 - Frequency of Data Collection*. *Vol. 2, Section 9 - Clinical Measurements* describes the procedures to follow for these measurements. Perform two trials each of the grip strength, timed chair stand, and timed walk. None of these measures form exclusion criteria for the WHI components other than they must be completed. Record the results on *Form 90 - Functional Status*.

4.4.5.6. Cognitive Assessment (HRT; Subsample)

Cognitive function will be measured in all HRT participants aged 65 to 79 at SV3 or earlier and at follow-up visits as outlined in *Vol. 1, Table 1-A1.1 - Frequency of Data Collection. Vol. 2, Section 9 - Clinical Measurements* describes the procedures to follow for these measurements. This measure does not form an exclusion criteria for the WHI components. Record the results on *Form 39 - Cognitive Assessment.*

4.4.6. Randomize Participant (Required)

Key-enter or scan forms completed at SV3.

Proceed with enrollment and randomization as described in *Vol. 5 - Data System, Section 6 - Eligibility Determination and Randomization.* Note that participants in both HRT and DM must be randomized to both components on the same day. Make sure the participant has completed all requirements for both components before randomizing her to either.

The Clinic Manager or Data Entry staff person (or other non-blinded staff), randomizes the participant and advises the appropriate non-blinded CC staff of the group assignment. The CCs are encouraged to have local procedures in place to blind Dietary Assessment and Clinic Practitioner staffs' knowledge of the participant's randomization assignment to DM.

After the participant is randomized to DM, welcome her to the study and present her randomization assignment without personal bias. Remind the participant not to reveal her randomization assignment to clinical staff.

4.4.7. Dispense Blinded Study Medications (HRT only) (Required)

- Dispense one HRT study pill bottle. (Six-month supply). See *Section 15.4.2 - Selecting and Dispensing* and detailed instructions in *Vol. 5 - Data System*.
- Ask participant if she wants a non-child resistant cap for her study pill bottle and obtain a signed release, if appropriate.
- Review each item of the *HRT Study Pills Instructions* in the *HRT Handbook* and offer a new *Handbook.*
- Inform the participant that you will be giving her a new bottle of study pills and that you will be keeping her old study pills (the ones dispensed at SV2). Do not tell her that you will be weighing her pills or that the pills she was taking were placebos. (See *Figure 4.15 - Suggested Script for Blinded Study Medication Dispensation).*
- Ask the woman to start taking her study pills that day if she did not already take one from the bottle dispensed at SV2; otherwise, she should start on the day after SV3.
- Instruct her to keep the study pills in a safe place in her home, out of the reach of children or animals.
- Give her a new *Form 53 - HRT Calendar (*if she has a uterus) and offer another *HRT Handbook*, if needed.

4.4.8. Exit Interview

Review the SV3 checklist to be sure you have completed all necessary tasks during the visit.

If the participant is not interested in or eligible for the CT, assess her interest in OS and complete *Form 11 - Consent Status* appropriately.

After completing all of the SV3 procedures and forms, spend a few minutes talking with the participant. This helps to establish rapport and create a commitment to the study. The appropriate means for building rapport depends on the participant. Be sensitive to the best way to bond individually with each woman.

For future contacts, it may be helpful to write informal contact notes in the participant file about her concerns, interests, questions or style of interacting.

Inform the participant of what to expect at her next follow-up contact (6 week phone call for HRT, semi-annual contact for DM) and other follow-up contacts. If desired, give each participant a copy of her contact schedule. (*WHIP 0472).*

Instruct the participant to contact the CC any time she has questions or concerns.

4.4.8.1. Participants Assigned to the DM Dietary Change Group

Participants randomized to the DM Dietary Change meet with a Nutritionist (or other designated non-blinded staff) to be assigned to a DM Dietary Change group. The Lead Nutritionist uses the considerations outlined in *Section 6.8.2 - Forming DM Intervention Groups* to make a list of potential group meeting times, defined by day of week, time and location. The Nutritionist (or other designated staff member) uses this list to assign DM Intervention participants to an available group. If a participant cannot attend any of the available groups, she

is placed on a waiting list. For details about the information to include on a waiting list refer to *Section 6.8.2 - Forming DM Intervention Groups*. The Lead Nutritionist should be notified when 8 to 15 women are assigned to a group.

4.4.8.2. Participants Assigned to the DM Comparison Group

After randomization to the DM Comparison group, a non-blinded staff person should review the requirements of the Comparison group and the importance of this group to the overall DM with the woman. The general strategy for the women randomized into the Comparison group is one of minimum interference with their customary diets while collecting nutritional data appropriate for comparison with the Dietary Change group.

At randomization, give to DM Comparison group participants a standard packet of health information material including a copy of the *USDA/DHHS Dietary Guidelines for Americans*. Examples of other health information brochures given to all participants at randomization are outlined in *Section 2.3.2.6 - Other Equipment and Supplies.*

Restrict responses to any dietary questions to provide only information from the *Dietary Guidelines*. DM Comparison participants must not be given any additional nutrition information, counseling, or resources such as health pamphlets with nutritional advice or the American Dietetic Association Consumer Information phone numbers. If a participant specifically asks for information or a referral, refer her to her primary care provider.

Remind the participants that they will be receiving an annual WHI newsletter.

4.4.9. DM Participants Identified in 4DFR Subsample

If at randomization the participant is identified as part of the subsample requiring *4DFR* documentation, ask the participant to meet with the Dietary Assessment staff. The Dietary Assessment staff obtains complete descriptions of food items, preparation methods, ingredients and portion sizes in the *4DFR*. See *Section 10 - Dietary Assessment*.

4.4.10. Baseline Welcome Packet

Give the participant a packet to welcome her to the WHI. Explain the contents of the packet as you give it to each participant and thank her for participating. Give the packet to the CT participants after randomization and to OS participants after they have been enrolled in OS. Provide any required baseline packet items at the first semi-annual visit or by mail if the item is not available at this time. The contents of the packet are as follows:

Baseline Welcome Packet

	HRT	**DM** Dietary Change	**DM** Comparison	**OS**
Required				
WHI folder	*x*	*x*	*x*	*x*
WHI magnet	*x*	*x*	*x*	*x*
WHI Exercise Brochure	*x*	*x*	*x*	
About Calcium in Your Diet Handout	*x*		*x*	optional
Membership ID Card (CC Specific)	*x*	*x*	*x*	*x*
Welcome Letters:				
Welcome to the Hormone Replacement Program of the WHI	*x*			
Welcome to the Dietary Change Group of the WHI		*x*		
Welcome to the Comparison Group of the WHI			*x*	
Welcome to the Observational Study of the WHI				*x*
USDA/DHHS Dietary Guidelines for Americans			*x*	
Optional				
Chart Stickers (component - specific)	*x*	*x*	*x*	*x*
Contact Schedule	*x*	*x*	*x*	*x*
Appointment Card (for the next visit)	*x*	*x*	*x*	*x*
Other NIH-approved health brochures	*x*	*x*	*x*	*x*

The CCC provides supplies for the required items to each CC (see *Section 2.3.1.2 - Supplies Provided by the CCC*). Chart stickers can also be ordered from the CCC. The NIH-approved brochures and ordering information are listed in *Section 2.3.2.6 - Other Equipment and Supplies*. You may select brochures from this list to include in the welcome packet. You may also include any CC-specific information that you provide to each participant such as CC contact information, local incentive, etc.

4.4.10.1. Health Care Provider Packet (Optional)

The participant's primary health care provider may be given chart stickers (labels) specific for the component(s) to which she has been randomized/enrolled (see *Appendix F.4.1*). These stickers may be distributed either by 1) mailing the appropriate sticker(s) to the provider directly from the CC with a cover letter explaining the study (see model in *Appendix E.1.5*), or 2) giving the appropriate sticker to the participant in her Welcome Packet, with verbal instructions that she is to give them to her provider when she next sees him/her. Before you send the sticker(s) to the participant's primary health care provider or the participant, affix a label with CC contact information (CC name and phone number) on the bottom of the chart sticker. You may want to provide the participant with a copy of the cover letter to give to her provider along with the chart stickers.

4.4.11. Schedule Semi-Annual Follow-Up Contacts (Recommended)

Schedule an appointment for the semi-annual follow-up visit for HRT participants and provide an appointment card, if desired. DM participants may have semi-annual contacts (phone, mail or visit) at CC discretion (see below). Explain to the participant that two weeks to one month before this contact she will receive in the mail

a packet containing *Form 33 - Medical History Update; Personal Information Report (WHIP 0441)* to update, and, if appropriate, a reminder card or phone call with the date and time of the CC visit.

If your CC is conducting semi-annual follow-up contacts with DM-only participants, inform the participant that she will be getting a follow-up phone call and/or mailing (depending on CC-specific procedures) in about six months (refer to *Section 16.2 - Semi-Annual Contact*).

4.4.12. Participant Materials (Required)

Make sure the participant leaves with all the materials you have handed out, including:

- Baseline Welcome Packet
- One bottle of HRT study pills (HRT) (Required)
- *HRT Handbook* (HRT) (Required to be offered)
- *Form 53 - HRT Calendar* (HRT; for women with a uterus) (Required)
- Report of screening tests (at CC discretion; may be mailed out)
- Appointment card for semi-annual visit (HRT, optional)

4.4.13. Enroll in Observational Study (OS) (Recommended)

Invite women who are not eligible for or interested in the CT to participate in the OS. See *Section 4.2.5 - Observational Study Participants* and *Section 8 - Observational Study* for procedures to follow for enrolling women in the OS. Participants enrolled in the OS at SV3 will complete the OS informed consent process and all baseline forms (including *Form 42 - OS Questionnaire*) at this time. Preferably, they will complete these forms at the CC, but may be allowed to take them home and mail them back.

4.5. Eligibility

The eligibility criteria for the CT and OS are listed in *Vol. 1 - Study Protocol and Procedures, Section 1 - Protocol, Section 4.4 - Study Population*. The criteria are grouped into inclusion criteria for all components, exclusion criteria for all components, and additional exclusion criteria for CT, HRT, DM, and CaD, specifically.

Vol. 5 - Data System, Table C.1. lists all the forms containing data items needed to determine eligibility for each CT component and the OS.

Vol. 5 - Data System, Appendix C.2. - Eligibility Criteria lists how each criterion is mapped to data from screening forms. Specific eligibility issues are discussed in the following sections.

The *Form 2/3 - Eligibility Screen* forms instructions also identify eligibility criteria on that form and items to update during SV3 before randomization.

4.5.1. Determining Eligibility

Determining a woman's eligibility for the CT or OS includes the following steps:

- Collecting data during all screening visits.
- Entering the data into WHILMA.
- Updating *Form 2/3 - Eligibility Screen* at SV3.
- Running the Eligibility Determination function in WHILMA (Task 910, 920, or 940, as appropriate.)
- Running randomization or enrollment function in WHILMA.

Vol. 5 - Data System, Section 6 - Eligibility Determination and Randomization gives detailed instructions for performing the eligibility determination and randomization/enrollment tasks in WHILMA.

Additional procedures involved in determining eligibility include handling women who are temporarily ineligible and performing follow-up of abnormal lab or examination results.

4.5.2. Definition of Postmenopausal Status

The procedures for classification of menopausal status will vary by age of the participant, hysterectomy status and whether she is currently on or has been on hormone replacement therapy. *Figure 4.8 - HRT Menopause Algorithm* and *Figure 4.9 - DM and OS Menopause Algorithm* show the steps in how the database determines menopausal status.

Note that CCs are not expected to (nor should they) definitively determine a woman's actual clinical menopausal status beyond the WHI algorithms, except to address possible safety and adherence concerns.

Menopause refers to the changes secondary to the loss of estrogen production because of natural ovarian function cessation (e.g., resulting from advancing age), surgical removal of both ovaries, or other causes of permanent ovarian function cessation (e.g., radiation, chemotherapy). In a woman with an intact uterus, menopause is signified by the cessation of menses or the monthly period. In general, there are three types of menopause that may occur:

1. A woman with an intact uterus and at least one ovary may stop having periods naturally or as a result of radiation or chemotherapy.

2. A woman still having menstrual periods may undergo surgery, which results in the removal of both ovaries (and usually the uterus, although this is not necessary for menopause). The surgery could involve the removal of only one ovary if the other one had been previously removed.

3. A woman may have her uterus removed, but not her ovaries, when she is still having menstrual periods; thus, she is still premenopausal even though her uterus has been removed and she no longer has periods. At some later point she will go through "natural" menopause, often evidenced by hot flashes, night sweats and other symptoms.

4.5.2.1. HRT Menopause Algorithms (Figure 4.8)

a) Women who have <u>never</u> taken hormone replacement

A hysterectomy more than three months ago, or absence of "natural" vaginal bleeding in a participant age 50-54 with an intact uterus for 12 or more months or in a participant age 55 or older for more than 6 months will classify her as postmenopausal and eligible for HRT.

b) Women not currently on hormone replacement (who have used HRT in the past)

Women who have used HRT in the past, but have <u>not</u> used hormones in the last three months, as defined on *Form 2/3 - Eligibility Screen*, are classified as postmenopausal and eligible for HRT.

c) Women currently (or within the last three months) on hormone replacement with or without intact uterus

A woman currently on hormone replacement (including prescription estrogen; progesterone in oral, patch, or cream form; or oral or injectable testerone) or who stopped HRT less than 3-months ago must undergo a full 3-month washout (under her physician's guidance). If she is free of severe menopausal symptoms* after a three month washout as reported on *Form 4 - HRT Washout*, the participant will be classified as postmenopausal and eligible for the HRT. If the participant does have severe post menopausal symptoms after the 3-month washout or is no longer interested in HRT, she will be ineligible.

Women on herbal preparations for menopausal symptoms should stop the preparations, but do not need to go through a washout period.

4.5.2.2. DM and OS Menopausal Algorithms (Figure 4.9)

a) Women who have never taken hormone replacement therapy are eligible for DM or OS if they have ever had a hysterectomy <u>or</u> if their last episode of vaginal bleeding was more than 12 months ago. Women whose last episode of vaginal bleeding was 7-12 months ago (if age 50-54 years) or six or less months ago (if aged 55-79 years) are not classified as post menopausal and therefore are ineligible for DM or OS.

b) Women who have <u>ever</u> taken hormone replacement therapy are eligible for DM or OS, even if they have had recent episodes of vaginal bleeding.

* Severe menopausal symptoms refers to symptoms off hormone reported as sufficiently disturbing to the participant that she would not be able to tolerate placebo. They include, but are not limited to, hot flashes, night sweats, irritability, and depression.

Figure 4.8
HRT Menopause Algorithm

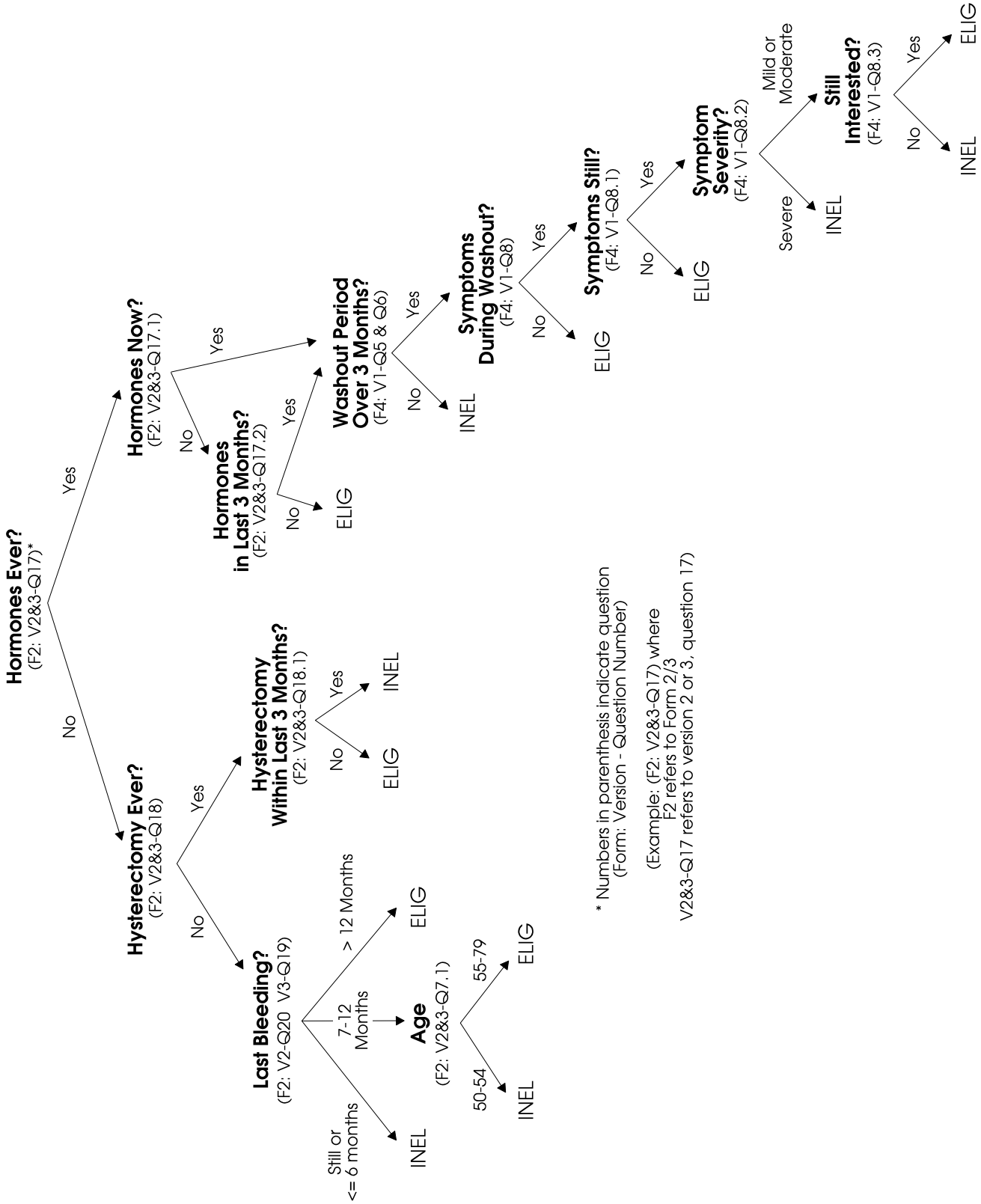
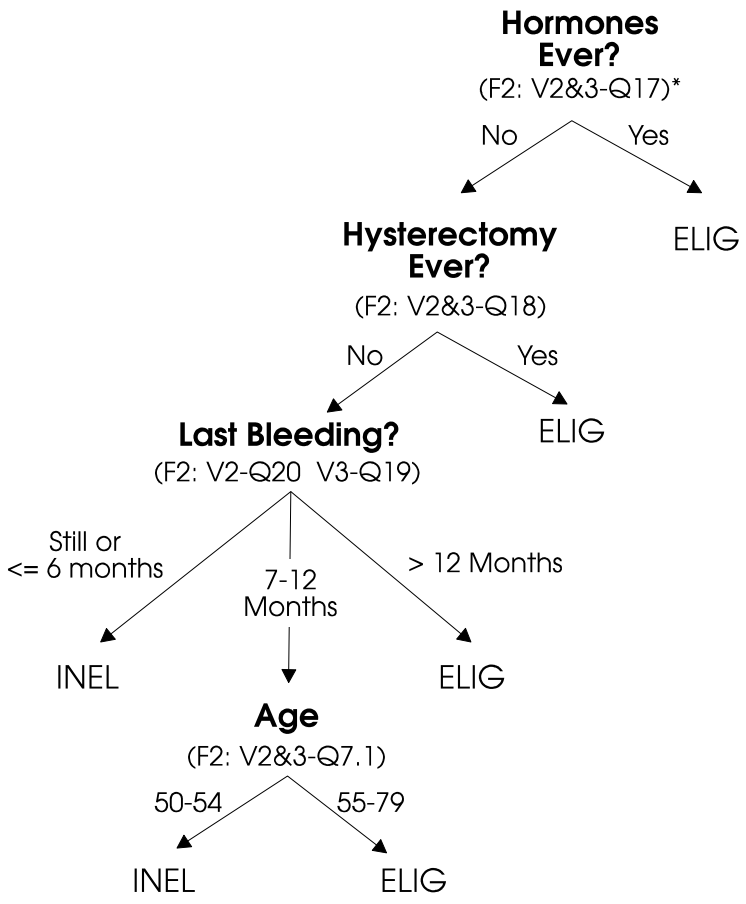


Figure 4.9
DM & OS Menopause Algorithm



* Numbers in parenthesis indicate question
(Form: Version - Question Number)

(Example: (F2: V2&3-Q17) where
F2 refers to Form 2/3
V2&3-Q17 refers to version 2 or 3, question 17)

4.5.3. Time Limits During Screening

In general, there is a 6-month limit on the time between SV1 and randomization to CT. You must repeat all baseline and screening data with an encounter date more than six months before the randomization date, with the exception of the following three forms:

- *Form 11 - Consent Status* for the Initial Consent (see below)
- *Form 2/3 - Eligibility Screen (see below)*
- *Form 60 - FFQ (*See *Section 4.5.4.3 - FFQ Rescreening)*

There is no expiration date on the Initial Consent. A participant never has to be reconsented for the initial consent regardless of the time since the encounter data.

If the encounter date on any form or task, excluding the three listed above, is greater than six months before the randomization date, you must recollect the data with a new encounter date before you can randomize the participant.

Recall that you must review *Form 2/3 - Eligibility Screen* for current accuracy at SV3 regardless of the time since the encounter date (see *Form 2/3 Form Instructions)*.

To recollect the data on all but the self-administered forms, complete a new form.

To recollect the data on the self-administered forms (*Form 20 - Personal Information, Form 30 - Medical History, Form 31 - Reproductive History, Form 32 - Family History Questionnaire, Form 34 - Personal Habits Questionnaire, Form 37 - Thoughts and Feelings*, and *Form 38 - Daily Life*) use the following procedure:

- Ask the participant to review her previously - completed form.
- Change the encounter date to the date you review the form with the participant.
- Update data items as needed, following the usual edit procedures as described in *Section 18.2.4 - Editing Forms*.
- Key-enter the corrections, including the encounter date and any other corrections.

WHILMA's eligibility determination calculates the time from the encounter date to the randomization date by subtracting the encounter date of the form or task from the current date. If the form or task is outside the time limit, WHILMA will return the message "[Name of Task] not entered" in the Criteria Determinations Block (see *Vol. 5 - Data System, Section 6 - Eligibility Determination and Randomization*) when you run an eligibility determination. This indicates that the task in question was not found with an encounter date inside the time limit. For example, if you collect Current Medications on January 1, 1994 and then attempt to randomize the woman on July 3, 1995, WHILMA will return the message "Current Medications not entered" in the Criteria Determinations Block. You must re-collect the data on Current Medications with a new encounter date before you can randomize or enroll the participant. See *Section 8 - Observational Study* for time limits on forms pending OS implementation.

4.5.4. Rescreening Ineligible Participants

4.5.4.1. Tasks to be Repeated Post-HRT Washout

Usually, data on screening forms are not collected before the woman completes her HRT washout. If for some reason they were collected before the hormone washout, you must repeat the data collection with a new encounter date (excluding the self-administered forms) after the woman completes her 3-month HRT washout. Baseline measurements are obtained after washout and before randomization to ensure that follow-up

measurements truly reflect intervention changes (e.g., hormones may affect cholesterol and triglyceride levels as well as some physical measures). You do not need to readminister any of the self-administered forms listed below that she may have completed before the HRT washout. For example, a woman may complete an SV1 and several self-administered forms such as *Form 30 - Medical History*. She may then decide she wants to go on an HRT washout to be eligible for HRT. You need to repeat the screening data collection you completed at the SV1, such as *Form 80 - Physical Measurements*, but you do not need to readminister the *Form 30 - Medical History*.

After the HRT washout, collect all baseline and screening data, except the self-administered forms listed below:

- *Form 2/3 - Eligibility Screen*
- *Form 20 - Personal Information*
- *Form 30 - Medical History Questionnaire*
- *Form 31 - Reproductive History Questionnaire*
- *Form 32 - Family History Questionnaire*
- *Form 34 - Personal Habits Questionnaire*
- *Form 37 - Thoughts and Feelings*
- *Form 60 - FFQ*

All baseline and screening data, excluding the self-administered forms listed above, must be collected after the participant completes her HRT washout, regardless of whether or not the encounter date for the original data is within the six months before randomization. If the encounter date for the original data is more than six months before randomization, you must recollect all the data as described in Part A above.

Recall that you must review *Form 2/3 - Eligibility Screen* for current accuracy at SV3 regardless of the time since the encounter date.

4.5.4.2. Ineligible on *Form 2/3 - Eligibility Screen*

If the woman is ineligible based on responses to questions on *Form 2/3 - Eligibility Screen*, stop the screening process. Do not conduct an SV0/SV1.

If the woman later becomes eligible, start the screening process again by completing a second *Form 2/3*. If the woman is now eligible by her responses to the second *Form 2/3*, schedule an SV1 and continue the screening process.

This *Form 2/3* rescreening procedure can only be completed for the criteria listed below. Use CC discretion and appropriate "future tickler" files to determine the time to rescreen for the criteria listed below.

Criteria on *Form 2/3* that can be rescreened:

- Age 47-49.
- Not likely to reside in area for three or more years.
- Active participant in another intervention trial.
- Colorectal cancer in the last 10 years (HRT only).
- Endometrial cancer in the last 10 years (DM only).
- Melanoma in the last 10 years (DM only).

- Other cancers in the last 10 years (except breast).
- Hysterectomy in the last three months.
- Pre-menopausal.
- Ten or more meals prepared away from home.
- Special diet for celiac sprue and other malabsorption syndromes.
- Low fiber, low-residue diet.
- DVT in the past six months.
- PE in past six months.
- Stroke in the past six months.
- TIA in the past six months.
- MI in the past six months.
- Medical condition associated with less than three years' predicted survival (e.g., lung disease, liver disease, heart failure).
- Lost 15 or more pounds in last six months.
- Can't come to the CC.

4.5.4.3. FFQ Rescreening

Women interested in the DM may complete a second screening FFQ (*Form 60*) one month after completing the initial FFQ if their initial screening FFQ (Form 60) is ≥ 29% and < 32% energy from fat (and their total energy intake is ≥ 600 kcal and < 5000 kcal.) A third FFQ is not allowed. The FFQ eligibility for women completing a second FFQ will use the same eligibility cutpoint (32%) as the initial FFQ.

This FFQ rescreening procedure is optional, at CC discretion. CCs are encouraged to consider the following when deciding whether or not to offer FFQ rescreening to a woman: (a) whether the CC needs this source of women to boost their DM recruitment, (b) clinic screening visit flow, (c) the 6-month screening visit window, and (d) staff resources. Clinics can decide whether or not to rescreen women on an individual basis when the FFQ eligibility report is run.

Note that this change to the FFQ rescreening procedure changes the minimum waiting time for rescreening on the FFQ from 12 months to one month, but limits the FFQ rescreening to women whose initial screening FFQ shows ≥ 29% and < 32% energy from fat (and total energy intake ≥ 600 kcal and < 5000 kcal.) To reduce the learning effect from repeating a task, CCs may choose to ask a woman to complete a second FFQ at a later time. This choice needs to be balanced with the 6-month screening window and the possibility of needing to recollect data.

We recommend that the Lead Dietary Assessment Nutritionist work with CC staff to train and implement these new procedures. Include training for all staff who work with the FFQ throughout the screening process.

4.5.4.3.1. Discussing the repeat FFQ option with screenees

CCs are encouraged to discuss the potential of completing a second FFQ with DM-interested women early in the screening process, ideally before they complete the initial FFQ.

Suggested script to use whenever the FFQ is first mentioned to a woman, e.g., during an in-person SV0 or to include with the cover memo you mail with *Form 2/3*, *Form 60* and *Form 61*:

"We occasionally ask women to fill out a second FFQ. This is a normal part of research. If we need you to fill out a second FFQ, it would usually be several weeks after you completed the first FFQ."

The reports that print out after each FFQ is scanned will not change. These FFQ scan reports will continue to print one of the following three messages:

- Eligible
- Ineligible: For calories
- Ineligible: For percent calories from fat

To determine which women are eligible to complete a second FFQ, you will need to run a DM eligibility determination in WHILMA for FFQ-ineligible women. You then run the *DM Eligibility Determination* report (*WHIP 0181)* for these women and the new CC report, *Members Eligible for FFQ Rescreening (WHIP 0741)*. After running these reports, Clinical Centers may decide whether or not to offer the FFQ rescreening option to a woman.

- DM Eligibility Determination Report.

The informational comment for "FFQ Pct Calories from Fat/Energy Intake" criterion on the *DM Eligibility Determination* report (*WHIP 0181*) has been modified to read "May be eligible for rescreening" for women whose percent calories from fat is < 32% and ≥29% and whose total energy intake is ≥600 kcal and <5000 kcal.

- The Members Eligible for FFQ Rescreening Report:

The *Members Eligible for FFQ Rescreening* report (*WHIP 0741*) lists all DM screening participants:

- Whose FFQ was scanned thirty or more days ago.
- Who have a daily percent calories from fat per FFQ ≥ 29% and < 32%.
- Who have not already completed a second FFQ.
- Who are not ineligible for DM for any other reason.

Suggested script when asking a woman to complete a second FFQ:

"We need more dietary information from you before we can continue your screening for the dietary part of the WHI. We will get this information by having you complete a second FFQ one month [or the time frame selected by the CC] from now. Our staff will schedule an appointment for you now.

Suggested script for telling women they are ineligible for DM:

"Based on DM eligibility criteria, you are not eligible for the dietary part of the WHI. We'd like to talk with you about being an important part of the Hormone Replacement Therapy study or the Observational study."

Clinics may choose to recontact women whose FFQs were scanned before March 15, 1996 and who were ineligible for the DM per FFQ, and who are not enrolled in the OS.

Suggested script for asking women to return to complete an FFQ after they have already been told that they are not eligible for the DM based on their first FFQ, i.e., women whose FFQs were scanned before March 15, 1996 and who are not enrolled in the OS:

"Some time ago you were contacted about participating in the Women's Health Initiative. We appreciated your interest in this important study and were disappointed when you were ineligible for the Dietary Modification study. There is a chance that you may be eligible now. We would like to offer you the opportunity to complete the enclosed FFQ and return it to the Clinical Center. We want to make sure that as many women as possible have the chance to participate in the Women's Health Initiative. Thank you very much for your help!"

4.5.4.4. Ineligible at SV1 or Later Screening Visits

If a woman is ineligible for the CT and OS based on data collected at any point during screening, stop the screening process at that point and do not conduct further screening visits. If the woman becomes eligible later based on that criterion, repeat data collection for the previously-excluding criterion and continue the screening process from the point at which you stopped. Repeat data collection for any data that exceed the time limits given in *Section 4.5.3 - Time Limits During Screening* above. Refer to *Section 4.5.4.3 - FFQ Rescreening* for specific details on FFQ rescreening criteria..

If the woman is ineligible for the CT based on criteria that can be re-evaluated (see list below), you can give her the option of joining the OS or waiting to see if she can become eligible for the CT at a later date. If you enroll a woman in the OS you cannot rescreen her for the CT. Keep in mind that women you rescreen may be poor compliers.

This rescreening procedure can only be completed for the criteria listed below. See the list for time restrictions on specific criteria. Use CC discretion and appropriate "future tickler" files to determine the time to rescreen for the criteria listed below.

Criteria at SV1 and Later

- Depression (*Form 6 - Final Eligibility Assessment*)
- Drug use (*Form 6 - Final Eligibility Assessment*)
- Alcohol use (*Form 6 - Final Eligibility Assessment*)
- Staff impression (*Form 6 - Final Eligibility Assessment*)
- No HRT or DM Consent (*Form 11 - Consent Status*)
- Current use of anticoagulants (*Task 44*) (Wait one week after stopping the anticoagulant before drawing blood.)
- *FFQ* - % calories from fat ≥ 29% and < 32% and total energy intake ≥600 Kcal and <5000 Kcal. (*Form 60 - FFQ*) (Refer to *Section 4.5.4.3 - FFQ Rescreening*)
- SBP > 200 or DBP > 105 (*Form 80 - Physical Measurements*)
- BMI < 18 (*Form 80 - Physical Measurements*)
- Suspicious CBE (*Form 84 - Clinical Breast Exam*) or Mammogram (*Form 85 - Mammogram*).
- Pelvic exam (*Form 81 - Pelvic Exam)*, Pap smear (*Form 92 - Pap Smear*), endometrial aspiration (*Form 82 - Endometrial Aspiration*), and transvaginal ultrasound (*Form 83 - Transvaginal Uterine Ultrasound*).
- HCT < 32% (*Form 100 - Blood Collection and Processing*)
- Platelet count < 75,000 cells/ml (*Form 100 - Blood Collection and Processing*)
- HRT enrollment adherence < 80% or > 120% (*Task 951*) (Can repeat enrollment adherence once if there is a good reason to believe the participant will not have further adherence problems after she is randomized.)

4.5.5. Waiver of an Eligibility Criterion

To try to minimize CC staff burden in evaluating eligibility, most criteria are assessed through closed-ended questions that are checked in the database. The questions themselves were designed to screen women as efficiently as possible while being true to the protocol definition. In some instances the eligibility criteria as determined by these questions are somewhat less flexible than the protocol. A waiver mechanism implemented by the CCC is available to address this discrepancy.

The Inclusion/Exclusion criteria from the protocol and other protocol restrictions on randomizations are listed below. Also listed is whether or not a waiver for the criteria will be considered. Some criteria are based on CC evaluation entirely (denoted by "CC") and thus no CCC intervention is needed. For temporary exclusions (denoted by "*"), CCs should follow the usual process for rescreening women rather than requesting waivers. (See *Section 4.5.4 - Rescreening Ineligible Participants* above.) If the rescreening does not resolve the situation, waivers will be considered only on those items indicated below. Waivers of safety criteria must be accompanied by adequate documentation of the reason the safety criterion is not a concern, such as correspondence with personal physician. (See examples given below in italics.)

Inclusion Criteria for All Components	**Waiver of Eligibility Criterion**		
	No Waiver Required - CC Staff Discretion	**CCC Will Consider Waiver**	
		NO	YES
*1. Postmenopausal female volunteers of all races and ethnicity, with or without a uterus or ovaries.		*x*	
*2. Ages 50-79 years, inclusive, at first screening contact.		*x*	
*3. Likely to be residing in study area for at least three years after randomization or enrollment.		*x*	
4. Providing written informed consent.		*x*	
A. Exclusion Criteria for All Components			
1. Competing Risk			
a. Any medical condition associated with predicted survival of less than three years in the judgment of a Clinic physician (e.g., class IV congestive heart failure, obstructive lung disease requiring long-term ventilation or supplemental oxygen in the past, sever chronic liver disease with jaundice or ascites, kidney failure requiring dialysis, sickle cell anemia).	*x*		
2. Adherence or Retention Reasons			
*a. Alcoholism	*x*		
*b. Other drug dependency	*x*		

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

Inclusion Criteria for All Components	Waiver of Eligibility Criterion		
	No Waiver Required - CC Staff Discretion	CCC Will Consider Waiver	
		NO	YES
*c. Mental illness, including severe depression	x		
d. Dementia	x		
*e. Active participant in any other intervention trial where participants are individually randomized to an intervention or control group. *Example: Woman responds that she is in a consumer products study and is randomly allocated to a given product with minimal additional time burden.*			x
B. Additional Exclusion Criteria for All CT Components			
1. Competing Risk			
a. Invasive cancer of any typein the past 10 years		x	
b. Breast cancer at any time (in situ or invasive)		x	
*c. Baseline mammogram or clinical breast examination findings questionable or suspicious of breast cancer		x	
*d. Acute myocardial infarction in past six months		x	
*e. Stroke or transient ischemic attack (TIA) in the past six months		x	
f. Known chronic active hepatitis or severe cirrhosis		x	
2. Safety Reasons			
a. Severely underweight (recommended limit of BMI < 18 kg/m^2 or unintentional loss of 15 or more pounds in previous six months)	x		
*b. Hematocrit < 32% *Example: Woman with thalassemia minor has low hematocrit. Since this is not an iron-deficient anemia, there are no safety concerns for DM. Document diagnosis of thalassemia minor and agreement of woman's provider to support participation.*		x (HRT)	x (DM)
*c. Platelets < 75,000 cells/ml		x (HRT)	x (DM)

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

Inclusion Criteria for All Components	Waiver of Eligibility Criterion		
	No Waiver Required - CC Staff Discretion	CCC Will Consider Waiver	
		NO	YES
Example: Woman has long-standing idiopathic thrombocytopeniawhich is stable in nature. No related conditions contraindicate participation in DM. Document nature of condition and agreement of woman's health care provider to support participation.			
*d. Severe hypertension (systolic BP > 200 mmHg or diastolic BP > 105 mmHg)		*x*	
e. Current use of oral daily corticosteroids		*x*	
3. Adherence or Retention Reasons			
a. Unwilling to participate in baseline or follow-up examination components such as mammograms, clinical breast exams, phlebotomy, electrocardiograms, questionnaires and form; or unable to complete baseline study requirements	*x*		
C. Additional Exclusion Criteria for Hormone Replacement Component			
1. Safety Reasons			
a. Endometrial cancerof any stage at any time		*x*	
b. Endometrial hyperplasiaat baseline biopsy or endometrial thickness > 5mm via ultrasonography (no rescreening)		*x*	
c. Malignant melanomaof any stage at any time		*x*	
d. History of non-traumatic pulmonary embolism or deep vein thrombosis, or deep vein thrombosis or pulmonary embolism ever	*x*		
e. Previous osteoporosis-related fracture being treated with HRT		*x*	
f. History of bleeding disorder serious enough to require transfusion		*x*	
g. Known history of hypertriglyceridemia, or lipemic serum leading to diagnosis of hypertriglyceridemia on baseline blood draw *Example: Woman with a recent bout of systemic infection (sepsis). Infection has resolved but triglyceride levels are still elevated (but resolving.) Document history and agreement of woman's health care provider to support participation.*			*x*
*h. Currently on anticoagulants		*x*	

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

Inclusion Criteria for All Components	Waiver of Eligibility Criterion		
	No Waiver Required - CC Staff Discretion	CCC Will Consider Waiver	
		NO	YES
i. Currently on tamoxifen		*x*	
*j. Abnormalities in baseline Pap smear, pelvic exam, or pelvic ultrasound (if performed)		*x*	
2. Adherence or Retention Reasons			
a. Severe menopausal symptoms that would make placebo therapy intolerable to the participant	*x*		
*b. Inadequate adherence with placebo enrollment (run-in) (less than 80% of daily pills taken) (only one repeat enrollment period is allowed)		*x*	
*c. Unable or unwilling to discontinue use of HRT (women must discontinue current replacement hormone therapy for at least three months before baseline measures for HRT enrollment)		*x*	
*d. Unable or unwilling to discontinue use of oral or injectable testosterone (must discontinue current testosterone use for at least three months before baseline measures for HRT enrollment)		*x*	
*e. Unwilling to have baseline or scheduled endometrial aspirations		*x*	
D. Additional Exclusion Criteria for Dietary Modification Component			
1. Adherence or Retention Reasons			
*a. Special dietary requirements incompatible with the intervention diet (such as celiac sprue, other malabsorption syndromes). Women will be eligible if they are on a diabetic dietor a low salt diet *Example: Woman has been prescribed a low fiber diet during acute episodes of malabsorption which happen infrequently (2-3 times per year) and last for less than a week. Except for these rare occurrences, the woman's normal diet would not exclude her from either the Dietary Change or Comparison Arms, justifying the waiver. Provide the CCC with documentation of the nature of woman's condition and the agreement of her health care provider in support of her participation.*			*x*
b. Colorectal cancerat any time		*x*	
c. Unable to complete Four-Day Food Record adequately	*x*		

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

Inclusion Criteria for All Components	Waiver of Eligibility Criterion		
	No Waiver Required - CC Staff Discretion	CCC Will Consider Waiver	
		NO	YES
*d. FFQ percent of calories from fat below a cut point chosen to exclude about 40% of screened women (may repeat assessment after one month if percent calories from fat is between 29-32 on first FFQ). FFQ energy intakes of < 600 kcal or >5,000 kcal at screening, regardless of percent energy from fat.		*x*	
*e. Number of main meals prepared out of home ≥ 10 per week	*x*		
f. Type I (insulin-requiring, ketosis-prone) diabetes mellitus			*x*
Example: Woman reports diagnosis of diabetes at age 12 and initiation of insulin therapy at age 15 causing routine exclusion as a type I diabetic. Medical records reveals this to be an early onset of type II diabetes found more commonly in Native American populations.			
g. Gastrointestinal conditions that contraindicate a high fiber diet	*x*		
h. Bilateral prophylactic mastectomy		*x*	
E. Additional Exclusion Criteria for CaD Component			
1. Competing Risk: The following "all components" and "all CT components" exclusion criteria will be reassessed just before randomization into the CaD component.			
a. Any medical condition associated with predicted survival of less than three years as described above (A.1.)	*x*		
2. Safety Reasons			
a. History of renal calculi		*x*	
b. History of hypercalcemia			*x*
c. Current use of oral corticosteroids		*x*	
d. Current use of calcitriol		*x*	
e. Unable or unwilling to discontinue use of vitamin D supplements more than 600 IU/day		*x*	
F. Other restrictions:			
1. Time limit on screening (6 months)		*x*(DM)	*x*(HRT)
2. Same day randomization for HRT and DM		*x*	
3. Completed baseline requirements (forms and procedures)			*x*

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

Inclusion Criteria for All Components	Waiver of Eligibility Criterion		
	No Waiver Required - CC Staff Discretion	CCC Will Consider Waiver	
		NO	YES
Example: Woman completes all aspects needed to determine eligibility above but refuses to provide some self-administered questionnaires after reminders and requests (e.g., Form 34 - Personal Habits Questionnaire or Form 37 - Thoughts and Feelings). CC determines the woman is an enthusiastic participant who wants to protect her privacy.			
4. Randomization within window of first annual visit for CaD			*x*
5. Limits on stratum enrollment (age, hysterectomy status)			*x*

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

If you identify a woman who fails to meet an eligibility criterion as determined by the database but who satisfies the protocol definition of that criterion as determined by the CC PI or Clinic Manager, do the following:

1. Assess the woman's eligibility for that component on all other criteria selected to date. To do this, review the eligibility determination report for the woman and assure that all other criteria are evaluated as "ELIG."
2. Send an eMail to the CCC Data Coordinator requesting a waiver of eligibility criterion. In this request, specify the following information: WHI participant ID number for woman, study component(s) for which she is being considered, eligibility criterion in question, a brief statement explaining the rationale for the request for the waiver, and the date of the scheduled SV3. This information will be forwarded to the CCC Project Directors for review.
3. Allow at least 24 hours (one working day) for CCC evaluation and processing. The CCC Project Directors will evaluate each request for consistency with the intent of the protocol. If submitted in time and approved, a waiver of a particular criterion for that woman will be made in the database by the CCC in time for the SV3 but usually no sooner than one working day from receipt of request. You are strongly encouraged to submit a waiver request well in advance of the SV3 (2 weeks or more) to ensure that processing is complete before the scheduled SV3.

The CCC will keep a log of all requests for waivers and their final disposition. All waivers will be documented in the database for monitoring purposes.

4.5.6. Closure of Recruitment Cells

The CCC alerts a CC PI by memo when the CC has reached a cell-closing threshold for a specific recruitment cell ("stratum") and specifies a date for closing the cell. The thresholds are as follows:

Cells	Threshold (% of recruitment goal)
DM Age 50-54	85%
DM Age 55-59	100%
HRT Age 50-54	105%
HRT Age 55-59	105%

After the specific recruitment cell has been closed, you may not be able to randomize a participant to the closed recruitment cell. When you run an eligibility determination (Task 910 or 920) for a participant in a closed cell, WHILMA will return a result of INEL (ineligible) with the following two exceptions:

1. Women who began screening before the cell closure (that is, they have a *Form 2/3 - Eligibility Screen* with a contact date before the date of the cell closure) will not be found ineligible. You may continue these women in the screening process and randomize them as usual.
2. Women from minority groups are not excluded by a specific, closed recruitment cell at a CC. You will be able to randomize minority women to a closed recruitment cell, even if the *Form 2/3* contact date is later than the date the recruitment cell was closed.

In addition, women who are going into both DM and HRT may be randomized into both studies, even if their recruitment cell is closed in either HRT or DM (as long as a cell is still open in one of those studies.) In these circumstances, CCs must request a waiver of eligibility for the study that is affected by the cell closure before you can randomize the woman (see *Section 4.5.5 - Waiver of an Eligibility Criterion*).

4.6. Randomization and Enrollment

All women to be studied in WHI will be officially randomized into the appropriate CT components (HRT, DM, CaD) or enrolled into OS. All components have eligibility criteria that must be met before randomization or enrollment (see *Section 4.5 - Eligibility*).

The purpose of the randomization and enrollment procedure is to confirm eligibility, randomly assign a woman to an appropriate treatment arm, and maintain the double-blind nature of the study (for HRT and CaD).

4.6.1. Randomization into CT

Randomization is the time at which a woman becomes a participant in a CT; when she is officially randomized in the study and assigned to a treatment arm. Women need to be fully consented and screened for eligibility before the time of randomization. A woman will always be included in the CT for the purposes of analysis after she has been randomized ("intent to treat" analysis), so it is important to verify her willingness and eligibility before randomization. Although a woman may withdraw from active participation in the study (perhaps because she is no longer interested or because of some potential adverse effects), she will be included in her assigned arm in the primary analysis when comparing treatment arms.

Neither the woman nor the CC staff should be able to influence or predict a participant's treatment assignment. It is very important that the details of randomization be kept confidential. By randomly determining the treatment assignment, potential imbalances between treatment groups are minimized. One general feature that can be revealed, however, is that the randomization will be stratified by CC, age of woman (50-54, 55-59, 60-69 and 70-79), and by hysterectomy status for HRT. Thus, the randomization will keep a percentage of women of a given age group in each treatment arm of a trial (HRT, DM, or CaD) close to the randomization fraction for that arm. WHILMA will carry out the randomization.

For statistical analyses, the day of randomization represents the starting point for determining the effects of the intervention. Survival time and incidence rates for all of the endpoints will be calculated from the date of randomization. Since there are three CT components, each with their own randomizations, the analyses could become quite complicated if all the randomizations could occur at any time. To simplify the analyses and their interpretation, randomization to HRT and DM must occur on the same day; randomization into CaD will occur at the first annual visit (within a $\pm$ 4-week window of the target annual visit) or at AV2 if CaD was not offered to a participant at the AV1.

The process for all components will involve a specification of the components in which the woman is willing to participate, a confirmation of eligibility for each of these components, randomization to treatment arm(s) or enrollment into the OS, and a production of confirmation of randomization/enrollment report and member contact schedule.

4.6.2. Enrollment into OS

These women must meet minimal WHI eligibility criteria (see *Vol. 1 - Study Protocol and Procedures, Section 1 - Protocol, Section 4.4 - Study Population)* and sign the *OS Consent* indicating their willingness to be followed. The OS may be considered to be a single-arm study, with automatic assignment to that single-arm when enrolled in the OS.

4.6.3. Randomization and Enrollment Procedures (Required)

Detailed instructions for performing the randomization or enrollment for each component (HRT, DM, CaD, and OS) in WHILMA are given in *Vol. 5 - Data System, Section 6 - Eligibility Determination and Randomization*. Additional issues you must consider for each component are described below.

DM and HRT randomization for a DM+HRT participant must be done on the same day. Be sure to run an eligibility determination for each component to ensure she is eligible for both before you randomize her to one of the components. For example, if the woman is interested in both HRT and DM, run an eligibility determination in WHILMA for both components before you randomize into either. After randomization, you will not be able to enter or edit any baseline data for either component. If you are missing data for the second component, you will not be able to enter it nor randomize the women to that component.

4.6.3.1. HRT Randomization

The HRT randomization is blinded so neither the participant nor the WHI staff will know to which arm the participant is assigned. Dispense blinded study pills according to procedures in *Section 15.4.2 - Dispensing HRT Bottles at SV3.*

4.6.3.2. DM Randomization

The randomization process is not designed for participants to watch, and CCs should not allow DM participants to watch the randomization process in WHILMA. Explain to the participants that the selection of the Dietary Change vs. Comparison groups is done randomly and that CC staff have no influence over the selection of the group.

Participants are randomized to DM Dietary Change: Comparison Group in a 40:60 ratio. Therefore, CCs should see more participants randomized to the Comparison group than the Dietary Change group.

CCs can randomize women together in small groups under special circumstances, as listed below:

- Introducing group randomization: CC staff cannot initiate or propose group randomization to a participant without some indication that she is seeking this option. The participant must bring up the concept and indicate that her participation will be changed, limited, or ended if she is randomized to a different group from the other woman or women.
- Size of group: Women can be randomized in groups of two to eight women.
- Reasons for group randomization: Any one of the following three reasons is acceptable for deciding to randomize women in a small group:
    - The women share the purchasing, preparation, or consumption of their food;
    - The women live together.
    - The women have limited transportation and must carpool to and from the CC; or
    - Other situations may be considered (contact the CCC for review).
- The entire group must be randomized together. You must complete all eligibility requirements for all women in the group before a group randomization is performed. If any women in the group are also in HRT, they must be randomized to HRT on the same day. Notify the CCC Data Coordinator at <u>least one working day before</u> the group randomization will take place. Provide the CCC with the member IDs of the participants in the group and approximate time the women will be at your CC.

4.6.3.3. CaD Randomization

CaD Randomization may first occur at the first annual (or second annual visit for participants not offered CaD at AV1) visit. (see *Section 7.1.5 - Randomization Activities*.) The CaD randomization assignment is blinded so neither the participant nor the WHI staff will know to which arm the participant is assigned. Proceed with dispensing CaD study pills, according to procedures in *Section 15.4.5 - Selecting and Dispensing CaD Study Pills.*

4.6.3.4. OS Enrollment

Observational Study enrollment may occur at any step in the screening process after the participant is determined to be eligible. See *Section 8 - Observational Study* for more details.

4.6.3.5. Remote Site Randomizations

Clinical Centers have three issues to resolve before performing remote site randomizations:

- randomizations into HRT and/or DM
- identification of the DM Intervention subsample for documentation of the Four-Day Food Record (4DFR)
- dispensation of HRT study pills

Two Options for conducting the remote site randomizations are given below. Clinical Centers must use the procedures given below, and may use one or both of these depending on the needs of the remote site. The same guidelines for off-site randomizations will apply for annual visits and CaD dispensation when those activities begin at remote sites in the future. For more information about remote site visits, see *Section 2.1.3 - Remote Sites.*

Option 1: Randomization in WHILMA after bringing forms back to the main site

1. Prepare for the remote site visit:
   - Run the eligibility determination and appropriate reports to determine all activities that need to be completed at the Screening Visit 3 (SV3). For example, check to see if the participant is in the Functional Status or Cognitive Assessment subsamples.
   - For an HRT participant, determine how many bottles of enrollment pills she has and whether she is on her first or second run-in attempt. Take a box of HRT <u>enrollment</u> pills to the visit in case the participant will need additional enrollment bottles. Record the dispensing of any additional enrollment bottles on *Form 955 - Enrollment HRT Dispensing*.
2. Complete the usual SV3 activities and collect the information as usual from the participant. Complete *Form 44 - Current Medications (Backup)* if the participant is taking medications not captured at SV1.
   - DM participants must satisfactorily complete the DM Eligibility Checklist review process and have an acceptable 4DFR before they are eligible for DM.
3. Tell the participant that you will need to complete some of the activities of the visit at the Clinical Center and arrange a time to discuss results of these procedures and expectations by phone, as needed.
   - For HRT participants, follow-up activities include dispensing a bottle of the HRT study pills. Take the HRT enrollment bottle from the participant, and tell her you will be mailing her a new bottle the next working day. (This means the participant <u>must</u> be randomized within one working day.) Briefly review the pill instructions with the participant before she goes home, and remind her that all data will be reviewed to ensure her safety before the next bottle of study pills are mailed out to her. Verify her phone number and address, and tell her you will call her in one week to be sure she had received her next bottle of HRT pills.
   - For DM participants, follow-up activities include documentation of the 4DFR, if selected as part of the 4DFR subsample, and administration of the DM Post-Randomization interview. Verify the woman's phone number and tell her that the phone interview will take about 30-45 minutes. Schedule a time during the next week for the phone interview and let her know the name of the staff person who will contact her. Give her the information in writing.
3. Return to the CC and with all participant data and perform the key-entry of appropriate forms.

4. Run the final eligibility assessment and resolve any eligibility requirements. Complete the randomization in WHILMA within 1 working day of the remote site SV3.

   - For HRT participants, select the HRT study medication bottle and mail the bottle to the participant along with a copy of the medication instruction sheet or HRT Handbook.
   - For DM participants, determine if they are included in the 4DFR subsample. If included in the subsample, mail them a copy of their completed 4DFR before the scheduled follow-up phone call and ask them to have the copy of their completed 4DFR and a set of measuring cups and spoons to refer to during the phone call.

5. Complete a follow-up phone call with the participant.

   - For HRT participants, call the participant within 4-5 days of mailing the HRT study pills and ask the participant if she has received the bottle and if she has any questions about taking the pills. Review the pill instructions with her.
   - For DM participants, call the participant at the scheduled time to document the 4DFR, as needed, and conduct the post randomization interview. To streamline the time on the phone, review the 4DFR and identify the questions to ask her before the call.

Option 2: Randomization completed in WHILMA at the main site while conducting the SV3 at the remote site

1. Prepare for the remote site visit:

   - Try to collect all the baseline forms (e.g., *Form 30 - Medical History Questionnaire, Form 31 - Reproductive History Questionnaire, Form 32 - Family History Questionnaire, Form 34 - Personal Habits Questionnaire, Form 37 - Thoughts and Feelings, Form 38 - Daily Life*) from the participant before the SV3 and scan them into WHILMA before the SV3.
   - Schedule the SV3 with the staff at the main site so someone will be available to key-enter the forms faxed to the main site.
   - Run the eligibility determination and appropriate reports to determine all activities that need to be completed at the SV3. For example, check to see if the participant is in the Functional Status or Cognitive Assessment subsamples.
   - Set up a file to leave at the main site containing necessary information, such as participant barcode labels and enrollment bottle numbers dispensed (for HRT), needed for completing the randomization process.
   - Ensure the participant file you take to the SV3 has sufficient forms and preprinted participant barcode labels.
   - For an HRT participant, determine how many bottles of enrollment pills she has and whether she is on her first or second run-in attempt. Take a box of HRT enrollment pills to the visit in case the participant will need additional enrollment bottles.

2. Complete the usual SV3 activities and collect the information as usual from the participant. Complete *Form 44 - Current Medications (Backup)* if the participant is taking medications not captured at SV1.

   - For HRT participants, take the HRT enrollment bottle from the participant. Count the HRT enrollment pills, and use the conversion chart of enrollment pills to weights *Figure 4.16 - HRT Enrollment Pill Count to Pill Weight Conversion Chart* Record the HRT enrollment bottle number and pill weight on *Form 10 - HRT Safety and Management Interview, Question 5*. As usual, if additional enrollment pills are dispensed, randomization cannot occur at this visit. Record the dispensing of any additional enrollment bottles on *Form 955 - Enrollment HRT Dispensing*.
   - DM participants must satisfactorily complete the DM Eligibility Checklist review process and have an acceptable 4DFR before they are eligible for DM.

4. Phone the main site to verify that you are requesting randomization of the participant, giving the participant name and participant ID number. Fax copies of the forms needed for eligibility to the main site (see the sample list below). Put a participant ID label with barcode on each page of the forms that are faxed. Cover or remove the participant's name any other personal identifier from all forms before faxing the forms. For example, cover the participant's name on the first page of the form with a post-in note (so uncover after faxing) and blacken out the name on the other pages of the forms. Using the model SV3 in *Vol. 2, Section 4.4 - SV3*, you would fax the pages of the following completed forms to the main site:

    - *Form 2/3 - Eligibility Screen* updates, first page and any updated pages
    - *Form 6 - Final Eligibility Screen*, 2 pages
    - *Form 10 - HRT Management and Safety Interview* (HRT), first page
    - *Form 44 - Current Medications (Backup)*, all pages
    - *Form 53 - HRT Calendar* (HRT), first page
    - *Form 62 - 4DFR* (DM), last page
    - Baseline forms not collected previously, first page and other pages as needed

5. At the main site, key-enter the faxed forms as you would routine forms. For example, key-enter:

    - Edits to *Form 2/3 - Eligibility*
    - All of *Form 6 - Final Eligibility*
    - Hormone Replacement Therapy enrollment bottle number and weight for the appropriate enrollment bottle, as recorded on the first page of *Form 10 - HRT Management and Safety Interview* (HRT)
    - All of *Form 44 - Current Medications* (Backup)
    - Encounter information on *Form 10* (HRT), *Form 53* (HRT), and *Form 62* (DM)
    - Encounter information and other pages as needed on other forms
    - Note that you will need to key-enter rather than scan any required mark-sense forms. Initial the fax copy of each form as it is key-entered.

6. Run the eligibility determination and resolve any eligibility requirements with the staff at the remote site. Randomize the participant as usual.

    - For HRT participants, select the HRT study pill bottle and mail the bottle to the participant along with a copy of the medication instruction sheet or HRT Handbook.

7. Phone the remote site to verify that randomization for the participant is complete, giving the participant name and ID number. FAX the randomization information, including DM intervention assignment and selection of 4DFR subsample, and the participant contact schedule to the remote site; and file in the participant's file.

8. Complete activities of the SV3:

    - For an HRT participant, tell her you will be mailing her a new bottle of study pills within one working day. Briefly review the pill instructions with the participant before she goes home, but remind her that all data will be reviewed to ensure her safety before the next bottle of study pills are mailed out to her.
    - For a DM participant, conduct the post randomization interview. For DM participants selected for 4DFR subsample, complete the 4DFR documentation and conduct the post-randomization interview.

9. After the visit,

- Complete data entry of the forms.
- Complete the follow-up phone activities with an HRT participants by calling her within 3-4 days of mailing the HRT study pills and asking it she received the bottle and if she has any questions about taking the pills.

4.6.3.6. DM Group Randomizations

Randomizations of DM-eligible participants who wish to be randomized as a group will be done by the CCC on the next working day following the participants' SV3 (or following the earliest date that all participants in the group are ELIG for DM in WHILMA.)

Procedure

1. **Before SV3:**
   - Notify the CCC via email of a group randomization at least one working day in advance of the SV3. If your two-digit Clinical Center ID number is 11-45, contact Elena Mullin; if your clinic ID number is 46-68, contact Gretchen Van Lom. Provide the following information:
     - Date of SV3.
     - Participant ID numbers of participants to be randomized as a group.
     - Name and phone number of person to contact at the CC about the randomization.
2. You will receive acknowledgment of your email from the CCC. If you do not receive acknowledgment within 24 hours (excluding holidays and weekends), contact the CCC by telephone to confirm that the email was received.
3. **At SV3:**
   - Collect and enter into WHILMA all participant data (including any subsample tasks that need to be performed before randomization)
   - If any of the participants are to go into HRT as well as DM, conduct all of the usual HRT SV3 activities (Vol. 2, *Sec. 4.4.4 – Guidelines for SV3 Activities*) except for randomization and study pill dispensation.
   - Run eligibility in WHILMA for all studies that the participant is to be randomized into (DM and HRT). When you receive an ELIG result for all applicable studies, tell the participants that you will need to complete some of the activities of the visit the next day and arrange a time to phone the participant. See Vol. 2, *Section 4.6.3.5 - Remote Site Randomizations, Option 1, step 3* for items to discuss with the participants.
   - **Do not randomize the participants to DM or HRT at SV3 .**
4. **On the next business day FOLLOWING the SV3**:
   - Run DM eligibility (task 910 in WHILMA for all participants). It is necessary to do this so that an eligibility determination result of ELIG for the current date is in WHILMA when the CCC does the group randomization.
   - When you have obtained a result of ELIG for all participants in the group, notify your CCC contact **by 10:00 AM Pacific time** via phone or email that the participants are eligible and ready to be randomized to DM. (If notification is received later than 10:00 A.M., the group randomization may not be completed until the following day.)

Note: If one or more of the DM group participants are going into HRT as well as DM, it is the CC's responsibility to randomize the participant to HRT on the same day she is 'group-randomized' into DM by the CCC. It is recommended that you obtain an HRT status of ELIG before contacting the CCC to proceed with the DM group randomization, and that you wait until the CCC has confirmed completion of the DM randomization before you proceed with the HRT randomization.

5. Randomization of the DM group by the CCC

- After receiving CC confirmation of the ELIG results for participants in the group, the CCC will complete the group randomization by noon Pacific time on that day. The CCC will notify the contact person at the CC of the DM treatment arm (and 4DFR subsample, if applicable) via email that same day as soon as possible following completion of the randomization.

6. CC Follow-up

- Mail appropriate post-randomization materials:
  - Send appropriate Welcome Packet to all participants
  - Send HRT pills to HRT participants
  - Send a copy of the baseline 4DFR to DM participants selected for the documentation subsample
- Complete a follow-up phone call with the participants:
  - For HRT participants, call the participant within 4-5 days of mailing the HRT study pills and ask the participant if she has received the bottle and if she has any questions about taking the pills. Review the pill instructions with her. Confirm with the participant that she has started taking the study pills.
  - For DM participants, call the participant at the scheduled time to documents the 4DFR, as needed, and conduct the post – randomized interview. To streamline the time on the phone, review the 4DFR and identify the questions to ask her before the call.

4.6.4. Back-up Enrollment and Randomization

If WHILMA is not working when you need to enroll or randomize a participant, enrollment or randomization may be completed by contacting the Data Coordinator at the CCC who will enroll or randomize the participant centrally. Central randomizations will be supported only in the case of extended loss of computer functions. Otherwise, explain the problem to the participant and let her know you will contact her as soon as randomization can be completed and will mail her study pills and/or DM assignment status (depending on the CT component in which she is interested).

Figure 4.10
Nomogram for Body Mass Index

Figure 4.11
Initial Consent Script

Suggested Script for Initial Consent

"Now that you have watched the video and have a general idea of what the study is about, there are several more things I'd like to go over with you. I'm sure you have some questions about the study, and this may answer those questions.

First, I'd like to repeat some of what you've just seen in the video. The Women's Health Initiative is a study of women aged 50-79 and has four parts: hormone replacement, dietary change, an Observational Study, and a calcium and vitamin D study that will begin next year. The part you join will be decided by you and the CC staff, based on the results of your tests and on the information about yourself that you provide on your forms. The study is funded by the National Institutes of Health (NIH). A total of 164,500 women from all over the U.S. will be in the study.

Joining the study is completely voluntary and you may drop out at any time. You may choose to answer or not answer any question on the forms. Any information that you give is completely confidential and will only be seen by WHI staff, and, if necessary, the Food and Drug Administration (FDA), no one else. All of your answers are grouped with the answers of other women in the study, and only this grouped information is reported. Your name and other personal information will not be released in any reports or publications.

To decide which parts of the study you can join, you will go through some screening tests and activities. These will take place over three visits to the CC. At the first screening visit, there are several things that will be done.

Your height, weight, waist, and hips will be measured over non-blinding undergarments, and without shoes. You will also have pulse and blood pressure taken after you have been sitting for five minutes. You will be told what your blood pressure is, and whether you need to see your doctor for your blood pressure. There should be no risk involved in any of these procedures.

Next, about three tablespoons of blood will be drawn from a vein in your arm. Sometimes a woman may get a bruise or, very rarely, an infection may develop at the site of the blood draw. We will do everything possible to avoid these problems. There is no more risk for having your blood drawn here at the CC than there would be if your blood were drawn in your doctor's office.

On the basis of these tests, we will decide which parts of the study you can join, and then it's up to you to decide which parts you'd like to join. We may find that you are able to join either the hormone replacement or the dietary part, or you may be able to join both. If you are able to join both, it is up to you to decide whether you want to join one or both parts. We would like to encourage you to consider joining both. If you are not able to join either the dietary or hormone replacement therapy part, you may be able to join the observational study. After your screening tests, we will talk with you about which part(s) of the study you are eligible for and interested in joining.

Remember you may contact the CC if you have any questions at any time while you are in the study. What questions do you have at this time?"

Figure 4.12
HRT Consent Script

Suggested Script for Hormone Replacement Consent:

There are several points about the Hormone Replacement Trial that I would like to go over with you. I'm sure you have several questions about this part of the study, and this may answer some of those questions.

First, as with all parts of the Women's Health Initiative, taking part in the Hormone Replacement Trial is completely voluntary and you may drop out at any time. You may choose to answer or not to answer any questions on the study forms. Any information that you give is completely confidential and will only be seen by WHI staff and, if necessary, the Food and Drug Administration (FDA), and no one else. All of your answers are grouped with the answers of other women in the study, and only this grouped information is released. Neither your name nor any other type of identifying information will be released in any reports.

All women will be taking study pills. Some women will be taking study pills that don't contain any medicine. Others will either be taking study pills containing estrogen alone or study pills that have both estrogen and progestin, depending on whether or not you have a uterus. Neither of these two kinds of study pills has been proven to be more beneficial or safe than the other. A computer makes the selection for the groups so that it is fair. No one knows beforehand who will be taking active hormones or placebo. Before you sign up you must be willing to take part in either group. Both groups are equally important to the results of the study since everything we learn will come from comparing the groups. Once you begin, no one can take your place in the study group to which you have been assigned.

In order to take part in the hormone replacement trial, there are more tests that you will have. These include a mammogram, an electrocardiogram or EKG, and a physical examination. The physical examination involves a breast and pelvic exam, and if you have a womb, a Pap smear to check for cervical cancer. If you have a womb, you will also need to have a test of the lining of your womb (called an "endometrial aspiration"). There is a small risk of infection, bleeding and puncture of the uterus from the endometrial aspiration.

You can join if there are no health problems that might make taking part dangerous for you. You will be placed by computer into one of the groups and given your bottle of pills. Neither you nor the CC staff will know to which group you have been assigned. However, if there is some kind of medical emergency, we can quickly find out which group you're in and get this information to your doctor.

When you join, you will be asked to take a pill every day without fail. If you have a womb, you will be asked to keep track of any bleeding from your vagina, how heavy the bleeding is, and on what days it occurred. Of course, many women will not have any symptoms at all, which is also important to know. Four to six weeks after your last screening visit, a WHI staff person will call you to see how you are doing.

Regardless of which group you are placed in, you will be contacted by the CC every six months and you will have follow-up visits at the CC at least once a year to see how you are doing and to pick up study pills. Each of these visits will last about one hour. You will also have physical exams once a year for the nine to twelve years you are enrolled in the study and a breast exam, review mammogram results, and gynecologic exam (if you haven't had a hysterectomy), to make sure that everything is okay. At these visits, measurements and lab tests similar to the tests you have already taken will be done. These tests will include height, weight, and blood pressure. There is a small risk of bruise or slight infections, at the site of the blood draw; however the risk is no greater than if your blood were drawn in a doctor's office. You will be asked to have a mammogram annually. A mammogram uses radiation, which may slightly increase the risk of developing breast cancer. Scientists of the WHI and the National Cancer Institute believe that this small risk is outweighed by the benefit of finding breast cancer early. Mammograms every 1 to 2 years are recommended for all women in your age group. You will also have ECG every three years. You may also have measurements of your waist and hip,

physical abilities, or concentration and memory, blood draws, and/or endometrial aspirations, every three years.

There are several side effects that can occur as a result of taking study pills. These include headaches, bloating, changes in bowel movements, irritability, anxiety, depression, vaginal bleeding, breast tenderness, sleep changes, and nausea. While side effects are common among women taking hormones, some of the symptoms you may have could actually be related to changes that come with aging or menopause. Not all of you will have symptoms, and for those who do, the amount and how often the symptoms happen will be different for each women. In most cases these symptoms are mild and are not harmful, but you should contact the clinic if any of the symptoms become severe or too uncomfortable. The minor symptoms associated with the study pills usually go away within six months of starting the study pills.

In rare cases, serious problems can occur from use of hormone pills, including cancer of the breast, uterus, stones in the gallbladder, or blood clots in the legs or lungs. [Show participant the table on the HRT consent.] However, the health care professionals here are very concerned about your safety and will be very careful with the procedures and will monitor regularly for early signs of more serious problems.

Remember, you can call the CC at any time throughout the study if you're having any problems or if you have any questions. What questions do you have?"

Figure 4.13
DM Consent Script

Suggested Script for Dietary Modification Consent:

"There are several points that I would like to review with you about the Dietary Program. I'm sure you have several questions about this part of the study, and this may answer some of those questions.

First, as with all parts of the Women's Health Initiative, taking part in the Dietary Program is completely voluntary and you may drop out at any time. You may choose to answer or not to answer any questions on the study forms. Any information that you give is completely confidential and will only be seen by WHI staff, no one else. All of your answers are grouped with the answers of other women in the study, and only this grouped information is released. Neither your name nor any other type of identifying information will be released in any reports.

In order to take part in the Dietary Program, there are more tests that you will have. These include a mammogram, an electrocardiogram or EKG a phyisical examination of your breasts by a WHI clinician.

Women in the Dietary Program will be placed by chance to one of two groups: a "Dietary Change" group or a "Comparison" group. A computer will make the selection. No one knows beforehand who will be in each group or has anything to do with what group you get. Before you sign up you must be willing to take part in either group, whether it is the Dietary Change group or the Comparison group. Both groups are equally important to the results of the study since everything we learn will come from comparing the groups. Once you begin, no one can take your place in the study group to which you have been assigned.

If you are placed in the Dietary Change group, you will attend regular group meetings. At these meetings you will receive advice on how to reduce the amount of fat that you eat and increase your servings of fruits, vegetables, and grains. These meetings will be held once a week for the first six weeks, every two weeks for the six weeks after that, and once a month for the next nine months. The meetings last about two hours. If you cannot attend a group session, you will be asked to make it up. In addition, you will be asked to keep careful records of the foods you eat as you change your eating patterns. That is what is required for the first year of the study. The total time this will take during the first year is about 36-40 hours in meetings plus travel time to the clinic. In addition, you will spend about one hour per day in home activities and recording the foods you eat. Starting in the second year and until the end of the study (about 8-12 years), you will attend group meetings four times a year.

If you are placed in the Comparison group, you will not be asked to make changes in what you normally eat. You will be contacted every six months, attend CC visits once a year, and will spend less than 10 hours a year in study activities.

Whether you are placed in the Dietary Change group or the Comparison group, you will be contacted every six months and make follow-up visits to the CC every year. At these visits, you may be asked to keep careful records of the food you eat and how they are prepared. There is a small chance someone might call you to ask about what you ate the day before. In addition, measurements and lab procedures similar to the screening tests you have already taken will be done. These may include pulse, blood pressure, height, and weight. You may also have clinical breast exams, electrocardiogram or EKG measurements of your physical abilities, and blood draws. There is a small risk of a bruise or slight infection at the site of the blood draw; however, the risk is no greater than if your blood were drawn in a doctor's office. You will be asked to have a mammogram at least every two years. A mammogram uses radiation, which may slightly increase the risk of developing breast cancer. Scientists of the WHI and the National Cancer Institute believe that this small risk is outweighed by the benefit of finding breast cancer early. Mammogram every one to two years are recommended for all women in your age group. The health care professionals here are very concerned about your safety and will be very careful with these procedures. There are no known risks associated with making the dietary changes.

Remember, you can call the CC at any time throughout the study if you're having any problems or if you have any questions. What questions do you have at this time?"

Figure 4.14
OS Consent Script

Suggested Script for Observational Study Consent:

"There are several points I would like to go over with you about the Observational Study. I'm sure you have several questions about this part of the study, and this may answer some of those questions.

First, I'd like to tell you about the purpose of the Observational Study. Many important women's health issue issues will be studied in this part of the WHI. We are interested in learning about what causes disease in women. We'd also like to see what health habits affect a woman's risk for getting heart disease, cancer, or broken bones.

We're hoping you will join the Observational Study. Some women join because they don't want to be in the other WHI programs, or because their screening tests showed that this part of the study would be the best choice. As with all parts of the WHI, taking part in the Observational Study is completely voluntary and you may drop out at any time. Any information that you give is completely confidential and will only be seen by WHI staff and no one else. All of your answers are grouped with the answers of other women in the study, and only this grouped information is released. Neither your name nor any other type of information about you will be given in any reports.

Women in the Observational Study will all be asked to fill out several questionnaires and forms at the start of the study. You may choose to answer or not to answer any questions on the study forms. Then, every year for the next eight to twelve years, you will be mailed forms like some of the one you have already filled out. These forms will ask questions about your health and any medical problems that may have happened in the last year. You will be given a stamped envelope to mail the forms back to the CC after you finish them. Once you join the study no one can take your place, so we'd like you to try to stay with the study for the entire time of the study.

In three years you will come back to the CC for a follow-up visit. At this visit, measurements and lab tests, like the screening tests you have already had, will be done. Your height, weight, waist and hips will be measured again, and your pulse and blood pressure will be taken. We will also draw a small amount of your blood for testing. There is a small risk of a bruise or infection when blood is drawn, but it is no greater than if your blood were drawn in a doctor's office. There are no other known risks associated with any of the things you will be asked to do.

A small number of women in the Observational Study will be asked to come in for another visit soon after the initial and three-year visit to repeat the same measures. The purpose of this visit is to help us learn about the precision of these measures.

Every year you will also be sent a newsletter. This newsletter will give you information about the progress of the study and will help us know that we still have your correct address.

Remember, you can call the CC at any time throughout the study if you're having any problems or if you have any questions. Do you have any questions now?"

Figure 4.15
Suggested Script for Blinded Study Medication Dispensation

Participant:

"How will I know which study pill I'm taking?"

Staff:

"You will not know which study pill you are taking and neither will we. If you have not had your uterus removed, you will be taking either a combination of progesterone and estrogen; or a placebo pill which means no active medicine. If you have had your uterus removed you will be taking either estrogen or placebo. The selection of which pill you take is done by chance much like the toss of a coin, selected by a computer."

Participant:

"Will I be taking a placebo pill at first?"

Staff:

"It's important to understand that this program is a research study. Because this is a study, there may be times that you are placed on a placebo pill for part of the study, and I will not be able to share with you when that time will be. There is also a chance you may be taking a placebo for the entire study."

If the participant still seems anxious about this information:

Staff:

"You seem anxious or concerned about what I just told you." (Hopefully, giving the participant time and patience to voice her concern will decrease her fears. However, if the participant still shows a lot of problem with this issue, it may be wise to choose not to enroll her into this portion of the study and interest her in one of the other choices.)

You should never disclose single- or double-blind information to a participant. As long as you explain this information as stated above, you are not lying to the participant and you are protecting the importance of the blinding process at all times.

It is very important to disclose this information before she signs the consent form. Then, as these questions arise again in six months or two years from now, the participant can again be reminded of what was initially said. Being consistent in your clinic (with all staff explaining this the same way using the same terminology) will help maintain the trust and comfort you want your participants to have.

Keep in mind that the randomization visit (SV3) means more to the CC than it does to the participant. The participant believes that she is in the study from the moment of signing the consent form and complying with your instructions to proceed. If the staff does not focus on the other changes that occur at this visit, the participant won't either, especially when a new bottle is dispensed.

4.6.5. Blinding Considerations and Recommendations

Blinding in the WHI involves several special issues that are unique to this set of trials. It is the intent of the WHI investigators and staff to minimize bias in trial results, thus necessitating blinding of participants and staff wherever possible. Because of the staffing configurations present in WHI CCs, maintaining staff blinding throughout the trial may pose a significant challenge.

4.6.5.1. Definitive and Effective Unblinding

Unblinding for HRT, DM, or CaD may occur definitively or effectively:

- Definitive unblinding occurs when the CC Unblinding Officer enacts the database unblinding function for HRT or CaD or when CC staff view specific database information (either in documents or on the computer screen) for DM.

- Effective unblinding occurs when a staff member or participant makes an educated guess about a participant's treatment (e.g., because of vaginal bleeding).

HRT is a double-blinded trial. The goal is to keep all CC staff, investigators, and participants blinded to study arm for the duration of the study. However, because of the signs and symptoms associated with female hormone use, there will be situations in which unblinding occurs, either definitively or effectively. All efforts will be made to keep the occurrences of unblinding to a minimum, while ensuring that participant safety is kept as a high priority.

DM is by its nature an unblinded trial. However, for unbiased ascertainment and adjudication of primary, subsidiary, and intermediate outcomes, it is essential to keep staff involved in ascertainment or adjudication of any of these outcomes blinded to trial arm. Because of the sharing of clinical duties among CC staff, this means the CC staff may also be definitively or effectively unblinded for DM women. However, the goal is that all CC staff other than the group nutritionists and dietary session staff should be blinded to treatment arm for the DM.

The CaD is a double-blinded trial. The goal for this trial is also to ensure complete blinding throughout the trial. Definitive unblinding should be extremely rare in this trial, although there may be a constellation of symptoms associated with CaD use that may result in participants or CC staff being effectively unblinded.

There are several ways in which definitive or effective unblinding can occur within specific WHI study components:

- HRT

  Definitive unblinding for investigation of symptoms/signs of pathology: Careful algorithms have been devised by WHI medical staff for the evaluation of symptoms such as vaginal bleeding. Each CC identifies an Unblinding Officer, who communicates unblinding results directly to the CC Consulting Gynecologist. The Consulting Gynecologist after becoming definitively unblinded, will direct the blinded CC staff as to appropriate management, thereby preserving definitive blinding of key CC staff (but not necessarily preserving effective blinding).

  Effective unblinding of CC medical staff doing gynecological exams: Because of the vulvar, vaginal, and cervical changes caused by female hormones, CC staff performing pelvic exams may become effectively unblinded to "active" or "inactive" study medications.

  Effective unblinding of participants and staff because such as vaginal bleeding: Because placebo study medication should not cause vaginal bleeding, women starting study pills who develop vaginal bleeding may become effectively unblinded to "active" or "inactive" study pills.

Adverse Effects: Definitive unblinding because of "serious adverse effects" may occur, such as in the case of primary care provider asking for treatment assignment of the management of certain medical conditions. In this instance, the Consulting Gynecologist may decide that only the primary care provider needs to be given the treatment arm information.

- DM

  Randomization: At SV3 the participant is randomized by CC staff member and receives a randomization report. The staff member performing the randomization will be unblinded, as will any staff member who is privy to the report at that visit or any report that includes DM treatment assignment as a data item.

  Participant in DM groups located at main clinic facilities: Effective unblinding of DM intervention participants may occur if they are seen by CC staff coming in group to meetings or if they call to cancel or reschedule intervention sessions.

  DM intervention nutritionists' files: The Group Nutritionists maintain files on all DM intervention participants. If these files are kept with other components of participant files or in any centrally accessible location, other CC staff may become definitely unblinded.

  Follow-up visits and activities: DM participants, if not warned otherwise, may talk about group issues at their follow-up clinic visits, resulting in effective unblinding of CC staff.

  Outcomes: If participants discuss their study involvement with their primary care providers, outcomes staff perusing medical files may become effectively unblinded if such discussions are filed. Participants also may call the CC between regularly scheduled visits to report outcomes, and may report their study arm at the same time, thereby effectively unblinding staff members.

4.6.5.2. Strategies for Maintaining Blinding

The following are required CC activities to maintain blinding:

- Ask DM participants not to reveal their randomization assignment to CC staff.
- Group Nutritionists are responsible for reminding/rescheduling DM Intervention participants and have access to DM Intervention files.
- Unblinding is requested by the Consulting Gynecologist and carried out by the Unblinding Officer. The Clinic Practitioner (CP) should note in the participant's contact notes that an unblinding occurred and the action recommended by the Consulting Gynecologist. However, the treatment assignment information provided to the Consulting Gynecologist is not provided to the CP or written anywhere on the participant's file. The Consulting Gynecologist should keep a brief written record of the circumstances, separate from the participant's file with her name, ID number, pertinent clinical information, and treatment recommendations and rationale.
- The same CC procedures are used for follow-up contacts (semi-annual or annual) with both DM Intervention and Control participants.
- Clinical Center staff who have authorized access to either the DM Intervention files or the HRT files are not involved in outcomes adjudication (assigning outcomes diagnoses).
- Clinical Centers document local blinding and unblinding procedures for HRT, DM, and CaD.
- Participants and CC staff will be asked at the close-out visit which arm they thought they were in.

The following are strongly recommended CC activities to maintain blinding:

- Prepare separate participant files for HRT forms (e.g., symptoms on *Forms 10* and *53*, gynecological exams on *Forms 81, 82,* and *83*, medication changes on *Form 54*) and contact notes and for DM Intervention forms (e.g., session data on *Forms 63, 64,* and *65* and session feedback on *Forms 70, 71,* and *72*) and contact notes.
- Follow-up dietary assessment and clinical assessment staff do not randomize participants to DM and do not have access to participants' DM Intervention or HRT files.
- Participants' general files should contain no notations, special colors, or special labels about DM intervention status. Database reports viewed by staff other than Group Nutritionists or DM Intervention support staff should have DM assignment blacked out.
- Develop signs and remind DM participants at follow-up visits not to tell CC staff their DM assignment.
- HRT and DM Intervention files should be kept separate from the participant's general file, preferably with access available only to authorized staff.
- Clinical Centers should identify a route to DM sessions that bypasses staff not involved in the DM Intervention.
- Clinical Center staff with authorized access to DM Intervention or HRT files should not be involved in outcomes ascertainment (requesting and compiling outcomes documentation).
- Outcomes ascertainment should be accomplished by a trained data entry or medical assistant staff person.
- Clinical and dietary assessment staff should not be involved in outcomes ascertainment.

- Do not file *Form 7 - Participant Status* in the participant's general file if unblinding would result (e.g., for DM participants), or as appropriate, file the *Form 7* in an area of the participant file to which the staff generally does not have access. Document in the contact notes that the participant's status has changed and indicate that a *Form 7* has been completed.

Figure 4.16
HRT Enrollment Pill Count To Pill Weight Conversion Chart

Number of Pills Remaining in Bottle	Weight in Grams to Enter into WHILMA
1	0.3
2	0.5
3	0.8
4	1.0
5	1.3
6	1.5
7	1.8
8	2.0
9	2.3
10	2.6
11	2.8
12	3.1
13	3.3
14	3.6
15	3.8
16	4.1
17	4.3
18	4.6
19	4.8
20	5.1
21	5.4
22	5.6
23	5.9
24	6.1
25	6.4

Number of Pills Remaining in Bottle	Weight in Grams to enter into WHILMA
26	6.6
27	6.9
28	7.1
29	7.4
30	7.7
31	7.9
32	8.2
33	8.4
34	8.7
35	8.9
36	9.2
37	9.4
38	9.7
39	9.9
40	10.2
41	10.5
42	10.7
43	11.0
44	11.2
45	11.5
46	11.7
47	12.0
48	12.2
49	12.5
50	12.8

Section 4
Screening

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SECTION 5

HORMONE REPLACEMENT TRIAL

INTRODUCTION

Hormone replacement therapy with estrogen or estrogen and progestin is commonly prescribed for women whose ovarian function is diminishing normally at mid-life or who have had their ovaries removed (oophorectomy). Women receive these exogenous hormones to control menopausal symptoms such as hot flashes, night sweats, or vaginal dryness, or to possibly minimize their risk of heart disease or fractures. It is the effectiveness of hormone replacement in preventing heart disease and fractures that the Hormone Replacement Therapy (HRT) component of the Clinical Trial (CT) seeks to investigate.

Women participating in the HRT component of the CT will be randomized in a double-blinded fashion based on the presence or absence of a uterus.

- Women with a uterus will be randomized to one of two arms:
  a) Conjugated equine estrogen (CEE) 0.625 mg per day + medroxyprogesterone (MPA) 2.5 mg per day continuously
  b) Placebo estrogen + placebo progesterone
- Women without a uterus will be randomized to one of two arms:
  a) Conjugated equine estrogen (CEE) 0.625 mg per day
  b) Placebo estrogen

Note: WHI will use formulations containing the CEE currently marketed as Premarin™ and the MPA currently marketed as Cycrin™.

Guidelines and requirements for implementation of the HRT component of the CT are included in this section. In addition, a *Consulting Gynecologist Handbook* containing HRT-related clinical procedures and guidelines, is provided in *Vol 2, Appendix H*. Each CC receives one copy of this *Appendix H* in a separate binder for use by the CC consulting gynecologists. Each Clinical Center (CC) may devise policies and schedules for themselves within these recommendations and requirements to produce optimal performance in the Women's Health Initiative (WHI) and quality care for its participants.

Clinical Center staffing for implementation of the HRT may also vary. Completion of physical measurements, interviewing, and follow-up tasks may be done by appropriately trained and WHI-certified medical technicians, medical assistants, interviewers, or RNs. Clinical tasks such as clinical breast exams, pelvic exams, and endometrial aspirations (EA), however, will require staff with the appropriate state licensure and supervision. (e.g., physician, nurse practitioner, physician assistant, registered nurse, or licensed practical nurse.) In addition to local *clinical* standards of care (not other research protocols), WHI certification is required for consistent data collection.

5.1 HRT Eligibility Issues

To be eligible for the HRT, women must meet the eligibility criteria for the CT as a whole. *Vol. 1 - Study Protocol and Policies, Section 1 - Protocol, Section 4.4 - Study Population* lists the additional criteria that a woman must meet to be eligible for the HRT. Most of these additional criteria are for safety reasons. It is the philosophy of WHI to avoid the administration of hormone replacement therapy to women who could be harmed by it. Each item of eligibility must be checked carefully before a woman is randomized into the HRT.

5.1.1 Informed Consent

A woman must sign the HRT consent form before you perform any clinical trial-specific activities. See *Section 4.2.4.9 - CT Informed Consent* for procedures for reviewing the HRT Consent Form with the woman.

5.1.2 Eligibility Based on Baseline Gynecologic Evaluations

5.1.2.1 Exclusions Based on Baseline Clinical Breast Exam Findings.

All baseline breast exams must be done by appropriately licensed (for clinical practice), supervised (if required), and certified WHI staff.

Women with findings that suggest possible malignancy on baseline breast examination will be temporarily ineligible for HRT until cleared by correlation with mammogram and/or ultrasound findings or clinical judgment and documentation. Tissue diagnosis will be necessary in some cases to establish a clear non-malignant status. Suspicious findings include masses that are new or changed or nipple discharge. Participants with these findings should be evaluated by the CC consulting gynecologist or their primary physician. If cancer is excluded, the woman is eligible.

Note that these exclusions are for all CT participants, including those interested only in DM. A normal mammogram report (or a follow-up to an abnormal mammogram that excludes malignancy) is a requirement before you can randomize a woman into the CT and for the woman to continue in the HRT component. (See *Vol. 2, Section 12 - Mammography*.)

5.1.2.2 Exclusions Based on Baseline Pelvic Exam Findings

All baseline pelvic exams must be done by appropriately licensed (for clinical practice) and certified WHI staff.

Women with findings that suggest possible malignancy on baseline pelvic examination will be temporarily ineligible for HRT until cleared. Vulvar, perineal, and vaginal findings that suggest possible malignancy include external lesions, ulcerations, or growths. Bimanual exam findings include uterine enlargement of greater than 12-week size or adnexal enlargement or masses. Participants with these findings should be evaluated by the CC consulting gynecologist or their primary physician, if they prefer. If cancer is excluded, the woman is eligible.

5.1.2.3 Exclusions Based on Baseline Pap Smear

All women interested in HRT must have a baseline Pap smear (endocervical smear in women with an intact cervix, vaginal cuff in women without a cervix). A Pap smear performed during the 12 months before SV2 will be accepted as baseline, if the cytology report can be obtained or if a verbal report from the performing physician's office is obtained.

Note that a woman who has had a subtotal hysterectomy may still have a cervix, and therefore should be followed regularly at years 3, 6, 9 and closeout.

The following classifications and actions are to be followed for the baseline Pap smear:

Classification	Eligibility Status	Further Action
Cancer (Invasive only)	Ineligible	Refer urgently to primary physician.
High-grade SIL (moderate dysplasia, severe dysplasia, carcinoma in-situ [CIS])	Temporarily ineligible	Refer to primary physician for evaluation. If cancer is excluded, woman is again eligible.
Low-grade SIL (mild dysplasia, atypical squamous cells, human papilloma virus)	Eligible	Inform primary physician of Pap smear results
ASCUS / AGCUS (Atypical squamous or glandular cells, undetermined significance)	Eligible	Inform primary physician of Pap smear result

Often for low-grade SIL or ASCUS, a second smear in 3 to 6 months would be recommended; some gynecologists do immediate colposcopy. These follow-up procedures to an abnormal Pap smear should not be done by CC staff or physicians, but should be referred to the participant's health care provider.

Note: CCs may decide to adopt more conservative guidelines than these.

In cases where the Pap report reads either "Insufficient material" or "No endocervical cells," the following guidelines should be used:

- If the Pap is from the vaginal vault, or if the woman has had a Pap smear at least once in the past and has not had dysplasia, this Pap result will be considered satisfactory and the participant will be eligible.
- If the woman has never had a Pap smear or has had dysplasia in the past, a repeat smear should be taken at the 6-month visit, but she will still be eligible.

5.1.2.4 Exclusions Based On Baseline Endometrial Evaluation

All women with a uterus interested in the HRT must have an endometrial evaluation at baseline that is classified as normal. Histological assessment is the preferred method of evaluation. Women may not *choose* to have a transvaginal uterine ultrasound instead of an endometrial biopsy. An endometrial aspiration or diagnostic D&C performed during the 12 months before SV2 will be accepted at baseline if pathology results can be obtained. A normal classification for the WHI baseline aspiration includes the following diagnoses by the local pathologist:

- No endometrial tissue identified
- Insufficient specimen
- Normal atrophic endometrium
- Normal secretory endometrium
- Normal proliferative endometrium

If endometrial fluid (quantity sufficient to fill the biopsy cannula, about 1.5 cc) is encountered at the baseline biopsy, and subsequent histology is benign, obtain a transvaginal ultrasound examination for the purposes of measuring the endometrial stripe and assessing the ovaries. If the total stripe width (exclusive of fluid) is ≤ 5 mm and there are no pelvic abnormalities, the woman is considered eligible for HRT.

If the pathology report reveals an endometrial polyp, and no other excluding diagnosis is present, no further evaluation of the endometrium is required for eligibility.

An abnormal classification for the WHI baseline endometrial aspiration is based on the following diagnoses by the local pathologist:

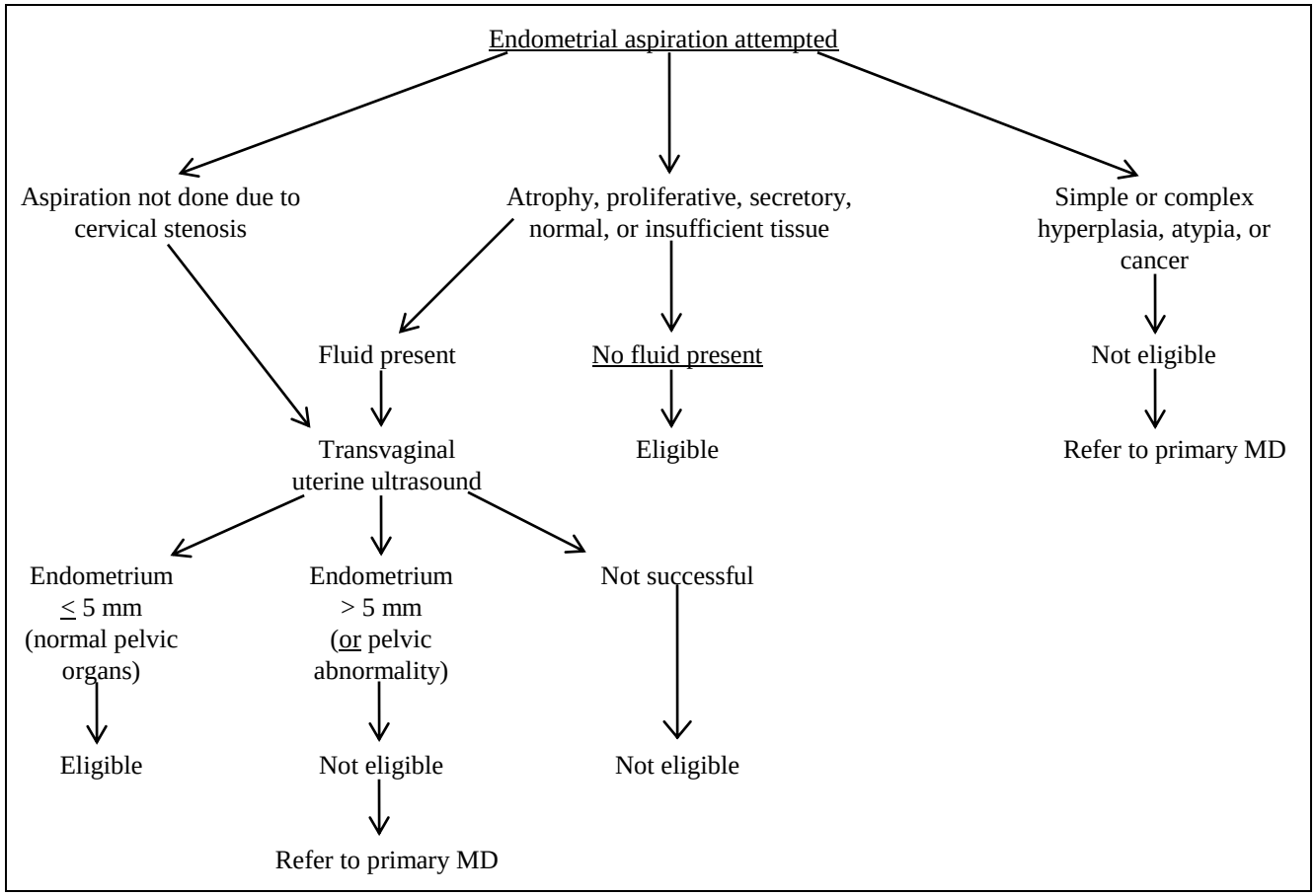
- Simple hyperplasia present
- Complex (adenomatous) hyperplasia present
- Atypia present carcinoma in-situ [CIS])
- Neoplasm, a cancer, present

Note: Women with any of the above diagnoses on baseline endometrial aspiration will be ineligible for the HRT. If the biopsy is investigated and found not to be endometrial cancer, the participant may be eligible for DM only. *Figure 5.1 – Baseline Endometrial Aspiration Actions* outlines actions to be taken based on the baseline aspiration. Note that the baseline endometrial aspiration will not have a central pathological review.

5.1.2.5 Exclusions Based on Baseline Transvaginal Uterine Ultrasound

If an endometrial aspiration is unsuccessful due cervical stenosis a second attempt should be made unless it is determined by the CC consulting gynecologist that it is unlikely to succeed. In that case, a transvaginal uterine ultrasound should be performed. An endometrial thickness ≤ 5 mm on the transvaginal uterine ultrasound will be accepted as normal and therefore the participant would be eligible for the HRT. If the endometrial thickness is greater than 5 mm, make a referral to her primary care provider. The participant may undergo a diagnostic D&C for increased endometrial thickness, and if the pathology report shows a normal result (see *Section 5.1.2.4 – Exclusions Based On Baseline Endometrial Evaluation*), the participant may be eligible. Transvaginal ultrasound measurement of the endometrial thickness may not be accurate if the uterus has either intramural or fibroids. Therefore, when the stripe cannot be measured uniformly due to this (or any other) problem, ultrasound only will not be considered acceptable as a baseline measure. If the baseline test is an ultrasound (unable to enter the uterus for endometrial sampling), and significant fluid is reported, the woman is considered eligible if the total stripe width (exclusive of fluid) is ≤ 5 mm and the pelvic structures are normal. If the transvaginal report reveals an endometrial polyp and no other excluding diagnosis is present, no further evaluation of the endometrium is required for eligibility. If neither the baseline endometrial aspiration nor the transvaginal ultrasound can be performed because of participant discomfort, inability to enter the vagina, or any other reason, the participant is ineligible for HRT.

Figure 5.1
Baseline Endometrial Aspiration Actions



5.1.3 HRT "Washout" Period for Screenees Already on HRT

Some women who are interested in participating in the HRT may be currently taking hormone replacement therapy. Women must be off hormone replacement therapy for three months before Screening Visit 1 (SV1) before they can be considered for participation in HRT. Therefore, women must washout of prescription estrogen or progesterone in oral, patch, injectable, or vaginal delivery (cream or ring) form, and oral and injectable testosterone (testosterone cream does not require a washout). Women who use herbal estrogen preparations should be asked to discontinue them, but a washout is not required. The hormone washout is to give women time to adjust to any symptoms they may have once they stop taking hormones. Some women will have severe persistent menopausal symptoms off hormone replacement therapy and are ineligible for the HRT because they would not be able to tolerate being randomized to placebo.

Women who report currently taking hormones during the initial screening interview will be instructed to see their primary physician or gynecologist if they are considering participation in the HRT. A letter from the CC explaining WHI, its goals, and the purpose of the washout may also be sent to the primary physician or gynecologist at this time (see *Figure E.1.4 - Model Letter to HRT Participant Health Care Provider*). They should discontinue their hormone replacement therapy only under the advice and guidance of their physician. Most women will need to be tapered off hormones by their physician to control withdrawal symptoms.

See *Section 4.5.4.1 - Tasks to be Repeated Post-HRT Washout* for women who initiate hormone washout after starting the screening process.

5.2 Initiating the HRT Intervention

The HRT intervention consists of the study pills, the *HRT Handbook, Form 53 - HRT Calendar*, and discussions with participants on the specifics of the intervention. (See *Appendix F, Figure F.3.2 - HRT Handbook*.) Use the four steps below when providing the study enrollment pills and the Handbook to each participant at the end of SV1 or beginning of SV2. Review them as necessary at subsequent contacts.

5.2.1 Step 1 - Introducing the HRT Intervention to the Participant

The following guide contains specific information on beginning the HRT intervention. Refer also to *Section 17.2.3 - Reasons for Poor Retention and/or Adherence* and *Section 17.2.4 - Strategies for Retention Challenges* for additional suggestions on helping a participant stay on study medications.

5.2.1.1 Providing the *HRT Handbook*

Welcome the participant to the HRT and congratulate her on her participation so far. Hand her a copy of the *HRT Handbook*. Explain that this handbook contains the basic information she will need and that you and she will cover some of that information right now. Tell her that if she ever has any questions she should ask them as you go along so that she will not forget them.

5.2.1.2 Reviewing the Importance of the HRT

Refer to the *HRT Handbook*. Review the importance of the HRT to women's health and to the field of prevention science. Remind the participant of her importance to the study and of her generosity in volunteering her time and effort. Discuss the scientific outcomes of the study (e.g., effects of HRT on heart disease and osteoporosis, who should take hormones, etc.) and why it is so critical to learn about cardiovascular disease in women. Also reassure the participant by emphasizing the many safety points in the HRT study. Use appropriate sections of the *HRT Handbook*.

5.2.2 Step 2 - Taking the HRT Study Pills

5.2.2.1 Instructions for Taking Pills

Give the participant her bottle of enrollment pills. Explain the label contents. Review the instructions for taking the HRT study pills as described in the *HRT Handbook*. These include what to take, when and how to take the pills, and how to store the pills. Include the fact that there are no special requirements about taking the pill with food, beverages, etc. Discuss what to do if taking the pills is difficult (e.g., swallowing). Ask the participant if she wants a non-child resistant cap. (If she does, see *Section 15.1.3 - Child Resistant Caps* for procedures for giving her one.)

5.2.2.2 Using the Pill Organizer

Give the participant a seven-day pill organizer and show her what it is for and ways to use it to remind her to take pills. Discuss using it for other pills she must take and remind her that the HRT study pill storage rules apply to pills in the organizer as well as pills in the bottles.

5.2.2.3 Designing a Reminder System

Ask the participant how she is going to remember to take the pill every day. Ask her about other pills or daily activities she has and how she remembers to do these things. Help her to integrate the HRT study pill with other daily pills or activities. If she (or you) seems concerned with her ability to remember, or if she indicates that she has had trouble in the past remembering to take pills or perform other daily activities, help her to design a cueing or reminder system to help her remember. Explain what a cue is (a cue is anything that will remind the participant to take her pill every day). Consider time of day, placement of cue or reminder, ease of seeing the cue, consistency of cue, etc., when designing the reminder system. Ask the participant how she will remember

to take her study pills when she is in an unusual situation (e.g., on vacation, traveling, weekends, etc.) Use appropriate sections of the *HRT Handbook*.

5.2.2.4 Identifying and Building Skills

Ask the participant if she thinks she will be comfortable performing all of the activities needed to participate in the HRT study. Clarify and discuss her areas of concern. Recommend specific behavioral goals and identify steps to achieve those goals. For example, remembering to take pills daily could include cueing the participant for a specific time and place to take the pill, having a supply of pills to take at that time and place, being assertive in order to take the pill in the presence of others, etc. Rehearse these new behaviors with her. Ask her to let you know how they worked at the next contact.

5.2.2.5 Review

Review all the steps involved in taking HRT study pills with the participant. Ask the participant questions that allow you to be sure she understands all the information and is ready to participate. An example of such questions include, "How are you going to remember to take your pills?" Remind her to call with any questions.

5.2.3 Step 3 - Understanding Symptoms

5.2.3.1 Identify Fears and Beliefs

Ask the participant what she is feeling about starting on the pills. Identify any fears, worries, or apprehensions that she may have about taking study pills. Ask her if she, her friends, or family members have had negative experiences with hormones. Ask her what she expects to happen to her and what the consequences of these events will be. Listen and acknowledge the participant's fears and beliefs about HRT, even if you feel they are unfounded. Correct any misperceptions she may have about the potential effects of HRT.

5.2.3.2 Reviewing Possible Symptoms

Discuss with the participant possible symptoms that she may experience. Indicate that each woman is different and that her experience may be the same or different from other women. Discuss her study pill to date, if appropriate. Emphasize the long-term nature of the program, including long-term gains and the fact that symptoms should be reduced by the end of the first year. Let her know that experiencing symptoms is normal and usually diminishes with time. Discuss with her the ways that the trial procedures promote participant safety and remind her that if she has any questions she should call the CC right away. Use appropriate sections of the *HRT Handbook*.

5.2.3.3 Review

Review the issues she brought up about her previous experiences and fears of HRT. Also, identify any issues about which you have more up-to-date information to allay her fears and concerns in the future.

5.2.4 Step 4 - Discussion of Routine Monitoring

5.2.4.1 Reasons for Monitoring

Explain to the participant the reasons for monitoring (e.g., ensuring the safety of the participant and collecting follow-up data).

5.2.4.2 Self-Monitoring

Show the participant with a uterus *Form 53 - HRT Calendar* and instruct her in its completion. Stress the importance of her regular completion of this form during the first year to track any bleeding she may have. Tell

her this form will also help to remind her to take her daily pills and that you will review this form together at her next CC visit.

5.2.4.3 Symptom Monitoring

Discuss the ways in which symptoms of HRT participants are monitored regularly. The current methods include *Form 53 - HRT Calendar, Form 10 - HRT Management and Safety Interview*, and many of the other questionnaires that each participant completes regularly. Indicate that these data will allow us to monitor the safety and progress of each participant in the HRT.

5.2.4.4 Clinical Monitoring

Discuss the various clinical monitoring activities that will occur throughout the trial, including gynecological exams. Discuss the endometrial aspiration with the participant. Inform her that a small number of participants will be asked to have an endometrial aspiration at follow-up visits. Refer to the *HRT Handbook*. Remind her that by doing these clinical monitoring activities, we will be able to better monitor safety and progress of the HRT.

5.2.4.5 Review

Review the basic schedule of follow-up and monitoring that occurs as part of the HRT. Ask the participant questions to determine if she understands her responsibilities and activities in the trial and the reasons for them. Ask her if she has any other questions at this time.

5.2.5 Randomization Visit

The randomization visit (SV3) is an important intermediate step in the HRT intervention. *Section 4.6.3.5 - Remote Site Randomizations* provides requirements and options for conducting remote site randomizations with HRT participants. Use the following three steps to monitor adherence and any symptoms during the enrollment period.

5.2.5.1 Step 1 - Weighing Pills

Ask for the participant's pill bottle at the beginning of the visit. Use the scale to weigh the remaining pills and record the pill weight in WHILMA using the procedures in *Section 15.6.22. - Bottle Weighing Procedures* and *Vol. 5 - Data System, Section 7.3.3.5 - Medication Adherence Collection*. Record the adherence rate on *Form 10 - HRT Management and Safety Interview* to use during the visit. Note that WHILMA does not take altered dose regimens into account. Do not weigh the pills in front of the participant or tell her that you are doing so.

5.2.5.2 Step 2 - Monitoring Adherence and Symptoms

At the randomization visit, women in HRT will participate in a short interview (*Form 10 - HRT Management and Safety Interview*). During this interview they will be asked about adherence patterns and strategies they may have used. This interview will continue to build rapport between participants and CC staff and ensure that worrisome symptoms are identified for each participant. (See the instructions for *Form 10- HRT Management and Safety Interview* for questions to be asked during this interview.)

Administer the interview using the following steps:

- Check the hysterectomy status of the participant in WHILMA by calling up the participant status screen or looking at a recent visit plan for the participant or asking the participant.
- Inform the participant that you would like to ask her a series of questions to help you keep track of her health.
- Administer *Form 10 - HRT Management and Safety Interview*.

- Review *Form 53* for report of bleeding.
- Refer the participant to the Clinic Practitioner as appropriate.

It is critical that you attend to symptoms a participant may describe at this point. She may report symptoms that are not due to study pills, but can be treated using the suggestions in *Section 5.4.1 – Minor Symptoms*.

5.2.5.3 Step 3 - Reviewing Key Points

Review the key topics of the HRT intervention at the randomization visit. Use the materials in *Section 5.2 – Initiating the HRT Intervention* steps 1-4 above, to guide the discussion. Key points include:

- Introduction and use of the *HRT Handbook*.
- Taking the study pills.
- Understanding symptoms.
- Routine monitoring.

5.3 Follow-Up Contacts with HRT Participants

5.3.1 Identifying Problems at Participant Contacts

Use every contact with a participant to identify issues or problems with regular pill taking or related symptoms. Use the materials in *Section 5.2 – Initiating the HRT Intervention*, Steps 1-4 above, to guide the discussion. Review *Section 15.8 - Managing Adherence* and *17.2.5 - Intensive Adherence Program* and develop strategies to improve pill taking behavior.

5.3.2 SERMs Handout

CCs are not required to give the handout *WHI Update – What You Should Know About SERMs* to participants. However, if CCs decide to give participants information on SERMS, they must use this handout. (See *Appendix F – Required CC Printed Materials, Figure F.3.10*.)

5.4 Managing Symptoms

Trial participants may experience adverse effects related to study interventions. These may range from mild inconvenience to life-threatening illnesses, or possibly death. Take great care to identify potential adverse experiences early so that appropriate and prompt treatment, referral, and study medication stoppage decisions can be made. Each of the CT components will have different expected adverse effects. Most of the adverse effects will be seen in HRT participants.

5.4.1 Minor Symptoms

5.4.1.1 Educate the Participant About Possible Symptoms

Several adverse effects are common among women taking hormone preparations, but other symptoms may be related to changes with aging or menopause. Not all women will have such symptoms, and the severity and frequency of symptoms will vary among women, as will the responsiveness of symptoms to hormone dose or regimen changes. When the participant starts on HRT study pills, inform her, by reviewing the HRT Handbook, of the various possible minor adverse effects that could occur. Tell her that these symptoms are in most cases not harmful, but that she should contact the CC if any of the symptoms become very uncomfortable or severe. Reassure her that the minor symptoms associated with HRT study pill use usually resolve spontaneously within 6-12 months of starting the medications.

5.4.1.2 Participants' Reporting of Minor Symptoms

Participants may report symptoms to CC staff in several different ways:

- Unscheduled or scheduled phone calls to the CC.
- Reporting symptoms to CC staff at the 6-week, semi-annual, or annual *HRT Management and Safety Interview* (*Form 10*).
- Recording in the "Notes" section of *Form 53 - HRT Calendar.*
- Responding to questionnaire items.

5.4.1.3 Initial Management of Minor Symptoms

The initial management of minor symptoms consists of palliative treatment, with the goal of keeping the participant in the original treatment arm. Many of these recommendations are included in the *HRT Handbook* (see *Appendix F, Figure F.3.2* for model) provided to the participant. Try these palliative treatments for a minimum of one month before initiating the dose step-down algorithm. Many women with HRT symptoms will be able to tolerate them with reassurance and simple relief measures.

If the participant experiences symptoms during the enrollment period, suggest the palliative measures described below. If the participant still experiences severe symptoms that she finds intolerable, complete *Form 11 - Consent Status* and mark that she declined further screening.

Discuss each minor symptom with the participant. The following steps may be used as guidelines:

- Ask about frequency, duration, and intensity, and record it on the "Notes" section of *Form 10 - HRT Management and Safety Interview*.
- Ask how much it interferes with daily activities.
- Give advice based on the guidelines below.
- Tell the participant that these symptoms are not health-threatening, but that she can call the CC should any of the symptoms become very uncomfortable or severe.
- Reassure her that these symptoms usually decrease after 6-12 months.

- Tell her that a CC staff member will call her back in one month to ask if she is still having any problems. Use a reminder system (tickler file or computer report) to track the calls.

WHI Clinic Practitioners (CPs) will not write prescriptions for treatment of symptoms, but may recommend over-the-counter medications, except aspirin. Vitamins should NOT be routinely recommended by CC staff for menopausal symptoms.

- Headaches: Recommend over-the-counter analgesics; i.e., acetaminophen (650 mg every 4-6 hours) or ibuprofen (200-400 mg every 4-6 hours). Before recommending ibuprofen or other non-steroidal anti-inflammatory drugs, be sure to ask the participant if any doctor ever told her not to take these medications or if she suffers from peptic ulcer disease or kidney failure. Do not recommend aspirin. If she has persistent or severe headaches, refer her back to her primary physician.
- Fluid retention, bloating, or change in bowel habits: Recommend dietary salt restriction, increased fluid intake, avoidance of caffeine (coffee, tea, chocolate and caffeinated cola beverage), and increased dietary or supplemental fiber intake. Do not prescribe diuretics. If a participant has fluid retention severe enough to warrant diuretic therapy, refer her to her primary physician. Such severe fluid retention will be a basis for review and, if persistent, for dose reduction or stopping the HRT.
- Irritability, depression: Determine sleeping and eating patterns. If symptoms are thought to be due to study medication, consider palliative measures (caffeine reduction, reduced salt intake, increased fluids, mild exercise and increased social activity). If these are ineffective, use the dose reduction algorithms described in *Section 5.4.1.4 – Step-Down Dose Management for Refractory Symptoms.* If the participant seems seriously depressed or if she or a family member is worried about her mood, she should be evaluated by a CP urgently. If you suspect that the participant has a depressive illness, refer her to her primary physician. If the CP judges the participant to be a danger to herself or others, make the appropriate emergency referrals. The following are suggested depression screening questions for the CP:

  "In the past two weeks or more, did you feel sad, blue, or depressed or lose pleasure in things you usually cared about or enjoyed?"

  If yes: "Have you felt sad or depressed much of the time in the past year, even if you felt okay sometimes?"

  "In the past two weeks or more have you thought that life isn't worth living?"
- Breast tenderness or swelling: Recommend caffeine (coffee, tea, chocolate) restriction and well-fitting, supportive bras. Recommend reduced salt intake and increased fluid intake. Reassure the participant that these symptoms usually resolve within two to three months.
- Sleep disturbances: Recommend mild exercise earlier in the day, caffeine and alcohol restriction, relaxing activity before bedtime, and avoiding heavy meals in the late evening. If you suspect a depressive illness, the participant must be evaluated by a CP. (See *Irritability, anxiety, depression* above).
- Nausea: Recommend that HRT study pills be taken in the evening or with food, to minimize problems with nausea. Consider referring the participant to her primary physician for further evaluation if the nausea is persistent, severe, or accompanied by vomiting.
- Vaginal discharge: Counsel the participant when starting study pills to expect some increase in vaginal discharge. However, the presence of foul odor, itching, dysuria, irritation or burning could be evidence of infection. These women should be referred to their primary physician for evaluation and treatment. Some women with a persistent irritating discharge may have atrophic vaginitis, which is usually treated with hormone replacement therapy. Recommend to the participants and their physicians that a non-estrogen vaginal lubricant (e.g., Replens, Astro-Glide, Lubron, K-Y jelly) should be tried initially. If the symptoms remain worrisome, the participant's physician will be asked to consult with the CC consulting gynecologist. If they (the Consulting GYN and the participant's provider) agree that local tissue stimulation by estrogen (delivery by cream or ring system) is indicated, the weekly dosage should be consistent with the published prescribing guidelines (e.g., PDR or patient package insert). Women who

are given vaginal estrogen cream by their physicians will remain blinded and on their assigned study drugs. Include the participant's use of vaginal estrogen products when you do the current medications update at the next annual visit.

- Increased skin pigmentation: Inspect any reported changes in skin color, and if warranted, refer the participant to her primary care provider.
- Muscle or joint pain: Recommend acetaminophen or an over-the-counter non-steroidal anti-inflammatory agent (if no contraindication exists). Do not recommend aspirin. If a participant has significant joint pain, swelling, or erythema, refer her to her primary physician.

5.4.1.4 Step-Down Dose Management for Refractory Symptoms

Figure 5.2 – Hormone Step-Down Management for Symptoms describes the step-down procedures to follow if a participant does not respond to the palliative treatments suggested above. Participants' dosage may be decreased to improve symptoms. After a month's trial, attempts should be made to advance to the original daily dose or the highest tolerable dose. Warn the participant that some spotting or bleeding might occur with the step-down, but should eventually decrease and/or stop.

Call the participant one month after reducing her HRT study pills to determine her response to the initial palliative management of her symptom(s). Document responses in the participant's file. If she reports continued symptoms, refer her to the CP.

You must complete a *Form 54 - Change of Medications* each time you add, change, stop, or alter the HRT study or open-label pills or dosage. Do not complete a *Form 54* for changes initiated by the participant that you have not agreed to.

1) Tell the participant to decrease her HRT study pill regimen to one tablet for five days of the week (e.g., Monday through Friday) and to continue in this manner for one month. Record the initiation of step-down in the participant's contact notes and on *Form 54 - Change of Medications*. Warn the participant that this change in pill schedule may cause the appearance of, or increase in existing vaginal bleeding. In one month, the CP should call to ascertain her response to the step-down dosing.

2) If the participant tolerates the altered dosing, gradually advance her back to the daily schedule: six days/week for two weeks; then seven days/week. If this is not tolerated, further step-down to every other day dosing may be started. The CP should call the participant in one month to ascertain her response to medication dose. If she does not tolerate the return to the full dose, tell her to return to the highest dosing schedule she can tolerate. Complete *Form 54 - Change of Medications* to reflect each new dosage.

3) If steps 1 and 2 are not tolerated, the CP should contact the CC's consulting gynecologist. Present the participant's symptoms and step-down response. The gynecologist will decide on treatment changes based on the participant's treatment arm. The CC consulting gynecologist can contact the CC Unblinding Officer who can execute a database function for unblinding and tell only the consulting gynecologist the participant's randomized arm. See *Vol. 5 - Data System, Section 6.5 - Unblinding Procedures* for a full description of duties of the CC Unblinding Officer.

   In rare cases, the CC consulting gynecologist will decide to change the participant's study pills or discontinue HRT altogether for refractory minor symptoms. Such decisions must be made in concert with the CC PI or their designee, who will not be made aware of the participant's identity during a decision about changing or stopping study pills.

4) If unblinding reveals to the consulting gynecologist that the participant is on active hormone, the CC consulting gynecologist (who is unblinded) and participant (who is *not* unblinded) must decide whether the symptoms are tolerable and she can continue her study pills, or if the participant cannot tolerate the symptoms and should discontinue her pills. If the participant is on placebo, the CC consulting gynecologist should refer her to her primary care provider, as her symptoms may reflect an underlying medical problem.

5) If unblinding reveals to the consulting gynecologist that the participant is on active hormone, the consulting gynecologist can change the participant's hormone regimen to manage these symptoms. (See *Figure 5.2 – Hormone Step-Down Management for Symptoms*.)

6) If the participant with a uterus tolerates a lower dose of MPA, then attempt to gradually advance her back to a daily schedule (PERT every day). If a participant cannot be completely advanced to PERT, the minimal amount of MPA 2.5 mg allowable is 3 pills/week.

7) If the participant with a uterus cannot tolerate any MPA, consider discontinuing her study pills.

For any referral back to the primary physician, a CC physician or CP will call the primary physician, send a letter or facsimile information, and describe the study to the physician. If the primary physician insists on stopping study pills, ask him/her to accept a step-down dosage first, and in either case to maintain the integrity of the double-blind randomization. The philosophy of WHI is that the CCs are not responsible for the primary health care of the participants. The CC physicians and practitioners will work in every possible way to maintain and foster each participant's relationship with her own source of primary medical care and to assist the primary physician with that individual's care. However, the CC will also make every attempt to avoid compromising the trial protocol, unless absolutely necessary for the safety of a participant.

5.4.2 Management of Menopausal Symptoms

Rarely, some women may continue to have postmenopausal symptoms after being randomized to study pills. This will be uncommon in WHI as all women who were previously receiving HRT will have been asked to washout of their previous HRT for three months before SV1. Those women who experienced severe postmenopausal symptoms after these three months were not eligible for the HRT component.

Management of continued postmenopausal symptoms will be done blinded. *Figure 5.3 - Continued Menopausal Symptoms Management* outlines the steps to be taken for management of postmenopausal symptoms on study medications:

1) Women complaining of intolerable hot flashes or night sweats will use palliative treatments (e.g., wearing cool, light clothing and avoiding stressful situations) for one month.

2) If their symptoms persist, increase their study pills to two pills per day for one month.

3) If she continues to have symptoms, consider stopping her study pills and referring her to her primary physician, as these symptoms could indicate other medical problems.

4) If the symptoms decrease, continue the two pills per day for two more months.

5) If the symptoms continue, decrease the regimen as necessary to one pill a day. If this is not tolerated, discontinue the study pills and refer the participant to her primary physician for evaluation.

6) Record each of the changes in study pill regimen on *Form 54 - Change of Medications*. If the participant stops using study pills altogether, a *Form 7 - Participant Status* should be completed.

7) Do not recommend vitamin or herbal therapy to alleviate menopausal symptoms.

Figure 5.2
Hormone Step-Down Management for Symptoms

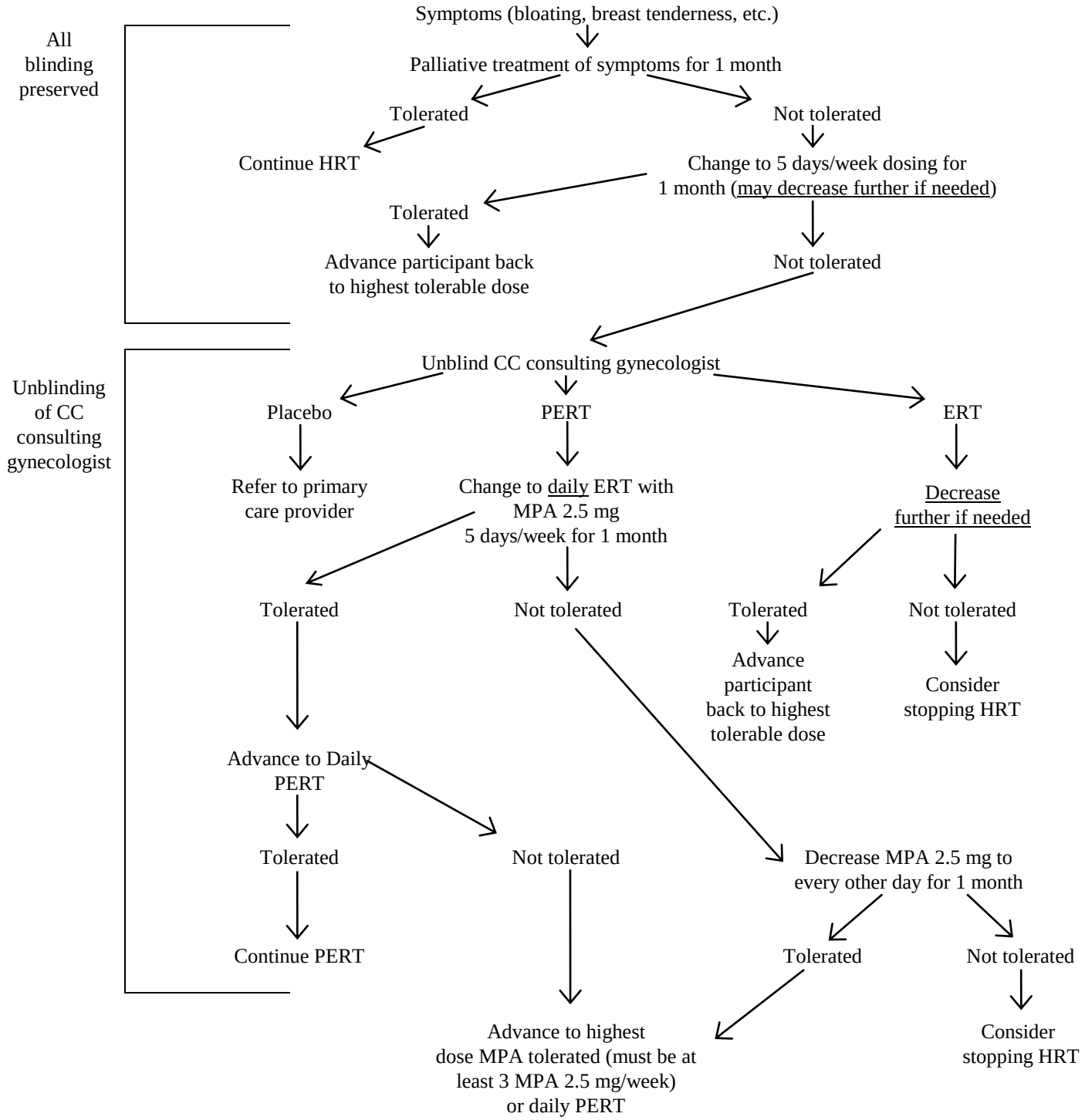
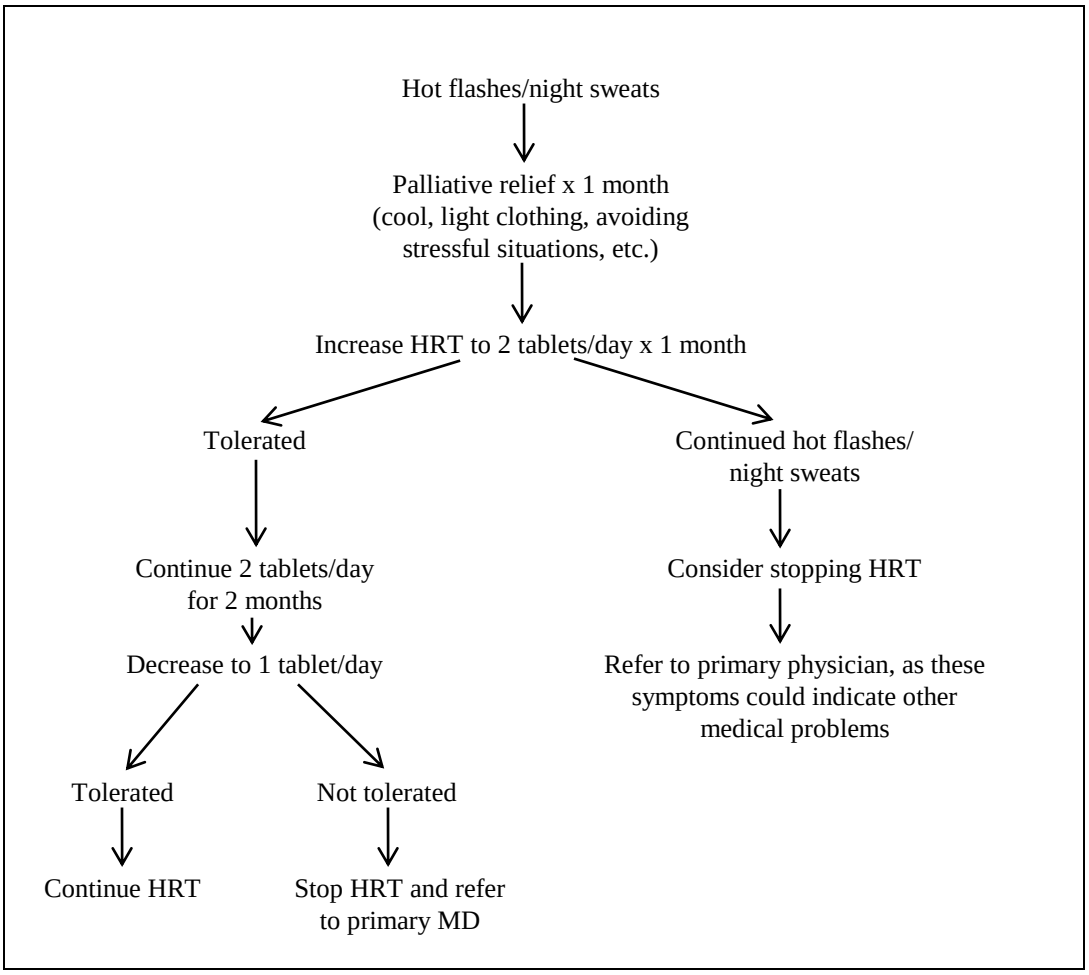


Figure 5.3
Continued Menopausal Symptoms Management



5.4.3 Management of Vaginal Bleeding

E-plus-P participants who present or report vaginal bleeding over 8 weeks from stopping their study pills require further investigation and work-up. CCs should perform an EA on these participants or the participants may have the EA and/or any further work-up with her outside provider. Any abnormal findings will require follow up and management by an outside provider.

Many women participating in the HRT who have not had a hysterectomy will experience vaginal bleeding at some time during the study. For women in the PERT arm, some amount of spotting is to be expected. However, the spotting usually begins to resolve by six to twelve months after starting HRT. Bleeding anytime after 6 months post-randomization into HRT will always need investigation to rule out endometrial disease. In HRT, only the CC consulting gynecologist will, if necessary, be unblinded to the study arm. This will aid greatly in making decisions about initial management of vaginal bleeding.

The management of vaginal bleeding will depend on (a) severity of bleeding, (b) time since randomization, (c) study arm assignment, and (d) endometrial histology. Consideration should also be given to how the endometrium was evaluated at baseline. See *Section 5.4.3.1 – When to Biopsy*.

Inform each woman who has not undergone hysterectomy that bleeding may occur after she starts the HRT study pills. She should call the CC if she has an episode of severe bleeding (bleeding heavier than her regular period used to be or eight or more pads/day). Have the participant speak to the CP, who will review the participant's file and ascertain the amount of bleeding, time since starting study pills, and history of previous bleeding. This CP will complete a non-routine *Form 10 - HRT Management and Safety Interview* (if contact occurs outside of a routine contact) and present the case to the CC consulting gynecologist, who will have access to the participant's file to determine the results, if any, of previous bleeding work-ups. The case presentation to the CC consulting

gynecologist will include the amount of bleeding, time since starting study pills, and history of bleeding since randomization.

Once a decision for treatment has been made, the participant will be called and either: (1) given a CC appointment for further evaluation during the same week, or (2) reassured and told when to return to the CC.

Participants who have not undergone hysterectomy will be asked to keep a *Form 53 - HRT Calendar* that they will bring with them on each CC visit during the first year post-randomization. The CP will review these calendars when the participant comes to CC visits before scanning. For evaluation of bleeding after the first year, CPs may choose to use *Form 53 - HRT Calendar* to monitor amount, pattern, and number of days of bleeding. However, this form does not need to be entered into the database after the first year.

If a participant has undergone a hysterectomy and reports vaginal bleeding, refer her to her primary care provider as soon as possible. If a participant who previously reported having a hysterectomy is found to have a uterus or uterine tissue, contact your CCC Data Coordinator Liaison before dispensing any HRT study pills. Present the case to the CC consulting gynecologist, who will decide if an endometrial biopsy is necessary. Manage the participant accordingly. (See *Section 9.9.2 – Performing the Pelvic Exam and Pap Smear.)*

5.4.3.1 When to Biopsy

The following procedures are established to avoid unblinding whenever possible, minimize the amount of staff unblinding, and avoid excessive aspirations. Given that most women have had an endometrial evaluation at baseline, bleeding equal to or lighter than a regular period (including moderate amounts of bleeding) during the first six months post-randomization will be assessed and managed by the CP without unblinding of the CC consulting gynecologist.

If bleeding warrants an EA and the participant refuses the exam, a TVUS is acceptable (the participant should not be offered a TVUS unless she refuses an EA). If she refuses both procedures, stop HRT study pills. HRT study pills may be restarted if she has either an EA or TVUS procedure and any abnormal findings are cleared.

- **Bleeding During the First Six Months Post-Randomization –**

  Women whose **baseline endometrial evaluation was by ultrasound** (and not a biopsy), and who bleed beyond three months after starting HRT should have an endometrial biopsy attempted, as biopsy provides a more definitive assessment of endometrial tissue.

  If the participant used a previous D&C or biopsy from an outside primary care provider, which could be more than six months old, ***more immediate evaluation may be necessary***.

  Heavy bleeding (greater than usual menstrual bleeding, or eight or more pads/day) during the first six months post-randomization requires that the CC consulting gynecologist be **unblinded** and direct management or refer to the participant's primary care provider as appropriate.

  – If the participant is in the **placebo** group, the CC consulting gynecologist should order an endometrial biopsy.

  – If the participant is in the **PERT** group and more than six months have elapsed since the last endometrial assessment (randomization was based on a previous D&C or biopsy from an outside primary care provider) a repeat biopsy will be obtained.

  Participants with **spotting or light to moderate** bleeding during the first six months post-randomization should be assured that this bleeding is expected and reassessed at the next scheduled semi-annual or annual visit.

- **Bleeding After the First Six Months Post-Randomization –**

  The CC gynecologist should be unblinded for all bleeding after six months.

  Heavy bleeding (greater than usual menstrual bleeding, or eight or more pads/day) after the first six months post-randomization requires endometrial biopsy. This bleeding may be due to fibroids or polyps.

Significant uterine findings should be referred to the participant's primary care provider for further evaluation and management.

Spotting or light to moderate bleeding should be presented to the CC consulting gynecologist who decides whether an unscheduled biopsy is necessary based on information from *Form 53 - HRT Calendar* (if available), endometrial evaluation record, and/or treatment arm.

- If the participant is in the **placebo** group, the CC consulting gynecologist should order an endometrial biopsy.
- If the participant is in the **PERT** group, had a normal baseline endometrial evaluation, and:
  - **bleeding is decreasing or staying the same, the participant should continue study pills and return for evaluation at next scheduled semi-annual or annual visit;**
  - **bleeding is increasing,** biopsy should be done.

5.4.3.2 Management According to Endometrial Histology

All results of diagnostic and subsample endometrial aspirations will be referred to the CC consulting gynecologist who will use the following guidelines to direct further management. Blinding of CC personnel, except for the CC consulting gynecologist, should be preserved.

CPs should keep in mind, however, that they should attempt to return the participant to the standard WHI dose regimen to keep altered dose regimens to a minimum.

PLACEBO Treatment Arm

- **Aspiration Not Done Due to Cervical Stenosis**

  CC consulting gynecologist will order an ultrasound evaluation.

  - If the endometrial stripe is less than or equal to 5mm, the participant will continue placebo therapy.
  - If the endometrial stripe is greater than 5mm, the participant should be referred to her primary care provider for further evaluation.

- **Normal, Atrophic, Proliferative, Secretory, or Insufficient Tissue**

  If the biopsy was done routinely, no unblinding or changes need to be made.

  If the biopsy was done non-routinely for bleeding, the participant may continue on her study pills. If bleeding persists, refer the participant back to her primary care provider.

- **Hyperplastic, Atypical, or Cancerous Results**

  If the participant has histologic results of simple or complex hyperplasia, atypia or cancer, discontinue all HRT study pills and refer her to her primary care provider. Send a copy of the pathology report to the participant's primary care provider.

  If a participant with hyperplasia without atypia is treated by her primary care provider, and her EA reverts to normal, she can re-enter the study.

PERT Treatment Arm

- **Normal, Atrophic, Proliferative, Secretory, or Insufficient Results**

  If the biopsy was done routinely, no unblinding or changes need to be made.

  If the biopsy was done non-routinely for bleeding, the participant should be reassured and continued for another three months on her study pills and then re-evaluated.

If the participant is bothered by the bleeding, the CC consulting gynecologist has the option of adding medication to attempt to decrease troublesome bleeding.

- For those biopsies showing an **atrophic** result, the CC consulting gynecologist can order an additional 0.3 mg of CEE daily for up to three months per year.

  Some participants who are put on additional CEE 0.3 mg daily will resume bleeding after the CEE dosage is reduced back to the standard regimen of CEE 0.625 mg a day (+ MPA 2.5 mg). For these participants, indefinite use of additional CEE 0.3 mg daily may be considered (*see Section 5.4.3.5 – Indefinite Use of Additional CEE 0.3 mg Daily*). Yearly endometrial surveillance will be required in these cases.

- For those biopsies showing a normal endometrial assessment within one year, the CC consulting gynecologist may administer a course of MPA 2.5-10 mg daily for three months.

  After this 3-month course, the CC consulting gynecologist will re-assess the amount of bleeding. If the MPA treatment led to decreased bleeding, the CC consulting gynecologist may prescribe another 3-month course of MPA for a total of six months of treatment.

  If after six months the bleeding is still decreasing, try decreasing the MPA dosage. Up to 5 mg of MPA daily may be continued indefinitely with re-evaluation every 6 months.

- For those biopsies showing a normal endometrial assessment within one year and continued bleeding unresponsive to other interventions, CCs may dispense open-label 5 or 10 mg MPA pills to HRT participants as "cyclic MPA" under specific circumstances (see below). This cyclic dosing should be used only as a "rescue therapy" for those HRT participants who have experienced persistent bleeding for at least 6 months and are asking to quit their study pills. Participants may also be placed on a cyclic regimen, so that bleeding patterns are predictable. Refer *to Section 5.4.3.6 – Use Of Cyclic CEE/MPA for HRT Participants* for guidelines for this regimen.

- **Simple and Complex Hyperplastic Results**

  Participants must be unblinded. Complete a *Form 54 – Change of Medications* for each change in study pills.

  - **Simple Hyperplasia**

    The participant may continue **PERT.**

    The CC consulting gynecologist will order MPA 20 mg/day for 3-6 months and repeat the biopsy.

  - **Complex Hyperplasia**

    The participant must stop **PERT.**

    The CC consulting gynecologist will order MPA 20 mg/day for 3-6 months and then repeat the biopsy.

  - **If repeat biopsy results in a report of no change in hyperplasia:**

    After the first 3-6 months of MPA therapy (and appropriate repeat biopsy, as above) - Increase MPA to 30 mg/day for another 3-6 months and re-biopsy.

    After a full 6-12 months of MPA therapy (and appropriate repeat biopsy, as above) - Stop PERT (if not already stopped) and refer to primary care provider.

  - **If repeat biopsy results return to normal after 3-6 months of MPA treatment:**

    Previous diagnosis of simple hyperplasia – Stop additional MPA, continue PERT.

    Previous diagnosis of complex hyperplasia – Re-institute PERT with additional MPA 2.5 mg/day for the remainder of the study. Re-evaluate every 6 months.

  - **If repeat biopsy results in a report of conversion from complex to simple hyperplasia:**

After the first 3-6 months of MPA therapy (and appropriate repeat biopsy, as above) – Treat with MPA 30 mg for 3-6 months and re-biopsy.

After a full 6-12 months of MPA therapy (and appropriate repeat biopsy, as above) - Treat with MPA 20 mg for another 3-6 months and re-biopsy.

– **If biopsy results in a report of <u>progression</u> of hyperplasia:**

CC consulting gynecologist should stop intervention and refer the participant back to her primary care provider who should decide if additional diagnostic procedures are warranted.

If a participant with hyperplasia without atypia is treated by her primary care provider and her EA reverts to normal, she can resume study pills.

Some women may develop an atrophic endometrium and bleed before the 3-6 months of MPA treatment are over. In these cases, if the participant has completed at least 2 weeks of MPA, it would be appropriate to decrease the MPA to 10 mg daily, and re-biopsy within a month. Treatment goals should include using a sufficient course of MPA to convert the endometrium to normal and avoid multiple re-biopsies.

- **Atypia or Cancer**

Discontinue study pills of participants with a histologic diagnosis of atypia or cancer and refer to their primary care provider. Send a copy of the pathology report to the participant's primary care provider.

5.4.3.3 Management According to TVUS Results

If an endometrial aspiration cannot be obtained or is refused, a TVUS is acceptable. If the TVUS results identify an endometrial stripe > 5mm, refer to the consulting gynecologist. Study pills may be continued if abnormal TVUS findings (stripe > 5mm) are cleared within 6 weeks. A subsequent normal EA or TVUS will clear an abnormal TVUS. Study pills must be discontinued if abnormal TVUS findings are <u>not</u> cleared within 6 weeks. Pills may be restarted once the abnormal findings are cleared.

5.4.3.4 Additional Guidelines for Managing Bleeding after First Year of HRT Study Pills

It is estimated that 20 to 30% of the participants will continue to bleed past the first 6 months to 1 year of taking HRT study pills. The CC consulting gynecologist is unblinded for all. Note that no open-label hormonal treatment should be initiated on participants in the placebo group. Options for management as described for bleeding after the first six months are described below:

- Add CEE 0.3 mg daily for a three-month period. Indefinite use may be considered if the guidelines in *Section 5.4.3.5 – Indefinite Use of Additional CEE 0.3 mg Daily* are followed. This regimen may help those participants who are spotting or bleeding due to an atrophic endometrium.

- Add MPA up to 10 mg daily for up to six months if the participant has been unblinded and has had a normal endometrial aspiration in the past 12 months. CPs may give lower doses of MPA for less than six months based on their clinical judgment.

- Participants may need long term daily MPA 2.5 - 5 mg to stop bleeding. If necessary, this may be started at any time during the study and continued indefinitely. However, this regimen should be assessed at each 6-month contact to attempt to return the participant to standard study regimen.

- Use cyclic regimen if bleeding persists and participant threatens to leave study. (Refer to *Section 5.4.3.6 – Use of Cyclic CEE/MPA for HRT Participants*).

- If a participant experiences heavy bleeding and does not respond to hormone treatment, then consider other possible causes of bleeding, such as polyps or fibroids, and make a referral to the participant's primary care provider, if appropriate.

All medication changes made by the CC should be recorded on *Form 54 - Change of Medications*, including return to standard regimen.

5.4.3.5 Indefinite Use of Additional CEE 0.3 mg Daily.

Some participants who are put on additional CEE 0.3 mg daily will resume bleeding after the CEE dosage is reduced back to the standard regimen of only CEE 0.625 mg a day (+ MPA 2.5 mg). For these participants, indefinite use of CEE 0.3 mg daily can be considered if either:

- The vaginal bleeding restarts after the three-month treatment period (of additional CEE 0.3 mg) is completed; **or**
- The participant indicates that she will discontinue her study pills if she is not allowed to continue on the extra CEE.

Although the expected risk of hyperplasia should be low, the CP caring for participants who continue on this regimen for more than 3 months should either:

- Increase the dose of MPA by adding open-label MPA 2.5 mg for a total dose of 5 mg daily; or
- Perform an endometrial aspiration if extra MPA is not used and the participant continues on the additional CEE for 9 additional months. An aspiration should be repeated on a yearly basis as long as the participant remains on this additional CEE regimen.

The decision to continue the additional CEE must be reviewed by the CC consulting gynecologist on a yearly basis.

5.4.3.6 Use of Cyclic CEE/MPA for HRT Participants

CCs may dispense open-label 5 or 10 mg MPA pills to HRT participants as "cyclic MPA" under specific circumstances (see below). This cyclic dosing should be used only as a "rescue therapy" for those HRT participants with uteri who have experienced persistent bleeding for at least 6 months and are asking to stop their study pills.

a. Identify Participants for the Cyclic CEE/MPA Regimen.

All of the following conditions must be met before CCs may offer an HRT participant a cyclic CEE/MPA regimen:

- The CC consulting gynecologist has been unblinded, knows the participant is on active PERT, and has evaluated and approved this course of action; *and*
- The participant is experiencing persistent (greater than six months), unpredictable vaginal bleeding and is willing to continue the intervention if the bleeding could be predictable; *and*
- Vaginal bleeding has not responded to the use of additional MPA and/or CEE as indicated in the HRT procedures in *Vol. 2, Section 5.4.3.4 – Additional Guidelines for Managing Bleeding After First Year of HRT Study Pills*; and
- The participant has asked to stop HRT study pills because of the bleeding.

b. Cyclic CEE/MPA Regimen

The cyclic regimen to be used is open-label CEE 0.625 mg every day with open-label MPA, 5 or 10 mg, added for the first or last 12-14 days of the month. The CC consulting gynecologist may decide on the exact dosage and duration of MPA based on an evaluation of the individual participant.

c. Implement the Cyclic CEE/MPA Regimen

Use the procedure below to select, dispense, and monitor the use of cyclic CEE/MPA:

- Discuss the participant's case with your CC consulting gynecologist, who will make the decision about implementing a cyclic regimen.
- Discuss with the participant the goal of a cyclic regimen (i.e., to help make the bleeding more predictable) and the administration schedule for this regimen. Remind her that bleeding, much like menstrual cycle bleeding, should occur 1-2 days after finishing the MPA for that month. Counsel her that this regimen does not mean she will stop bleeding entirely. If she agrees to try this regimen, continue with the procedures below.
- Collect her remaining HRT study pills and bottles and do an adherence collection in WHILMA on her remaining HRT study pills.
- Do not unblind the participant to her original treatment assignment. You may explain to her that only the CC consulting gynecologist knows her treatment arm and feels that this change will be a safe way to make her bleeding more predictable.
- Dispense only a six-month supply of the open label pills at this time: 2 bottles of open label CEE 0.625 mg and one bottle of MPA 5 or 10 mg. If her next routine visit is scheduled less than six months form the date of dispensation, collect the dispensed bottles at that routine visit and dispense a new six-month supply.
- Remind the participant when she should take her MPA by marking the designated dates of MPA (progestin) doses for the next six months on the participant's WHI monthly calendar pocket planner (annual incentive item). Emphasize that she will be taking two different pills on certain days of the month (specify days according to the CC consulting gynecologist's decision).
- Ask the participant to complete a *Form 53 – HRT Calendar* for at least the first year after starting cyclic therapy. This will help both her and the CP track vaginal bleeding pattern. (This information does not need to be data entered.)
- Provide the participant with appropriate pill-taking instructions. Tell the participant the actual dates that she should take the medication and that there will be pills left in the bottle. She will need to return the pills and the bottle at her next visit.
- Contact the participant after her first cycle (approximately 34-40 days after the open label pills are dispensed) to assess how she is doing. You may complete a *Form 10 – HRT Management and Safety Interview* at this time.
- Schedule or confirm her next follow-up contact at the appropriate time (semi-annual or annual). Consider contacting her at regular intervals in addition to routine contacts in the future as needed.
- Assess the need to continue the cyclic regimen at every routine contact. The decision to continue cyclic therapy or to resume the standard study pill regimen is left to the discretion of the local CP or CC consulting gynecologist.
- Complete a *Form 54 – Change of Medications*.

5.5 Problems That May Affect Continuation of Study Pills

Major adverse effects associated with HRT are those that are potentially detrimental to the participant. Depending on the severity of the effects, the CC consulting gynecologist may elect to stop study pills temporarily or to stop them permanently (only if absolutely necessary). Very few incidents are expected to be so severe that stopping the study pills will be necessary in either the short or the longer term. Major adverse effects will be communicated to the CC in various ways:

- Participant reports condition or event to CC staff at the 6-week HRT follow-up phone call.
- Condition or event is reported on *Form 33 – Medical History Update*.
- Participant reports condition or event to CC staff at a regularly scheduled semi-annual or annual contact.
- Participant reports condition or event at a non-routine CC visit.
- Participant, family members, or primary care provider calls the CC.

Some major adverse effects will have been resolved by the primary care provider by the time the CC is alerted. In such a situation, the study pills may have already been discontinued (or not stopped at all), particularly if the primary care provider has not been fully aware of the trial requirements. In these cases, because the participant has not been unblinded, the participant, with her primary care provider's agreement, may be restarted on HRT if the condition does not contraindicate use of hormones by trial protocol (or the participant may need to stop her study pills). See also *Section 5.5.6 – Guidelines for Restarting a HRT Participant Who Discontinued Pills for 12 Months or More* and *Section 5.5.7 – Guidelines for Restarting HRT Study Pills for a Participant Who Has Had a MI or Stroke.*

Educate the participant on the conditions that do **require** stopping study pills (see *Section 5.5.3 – Health Problems That Require Temporary Discontinuation* and *Section 5.5.4 – Health Problems Requiring HRT Termination)* and stress the importance of contacting the WHI clinic at the time they occur to ensure safety issues are addressed and to minimize scenarios as the one described above. Complete *Form 7 – Participation Status*, as appropriate. Distribute the HRT Handbook annually to all HRT participants.

5.5.1 Management of HRT After Hysterectomy for Non-Cancerous Condition

Some women in the trial will undergo a hysterectomy for reasons other than cancer, such as persistent bleeding from hyperplasia or fibroids. If a woman is to undergo a hysterectomy, she should inform the CC beforehand. Obtain the reason for hysterectomy from the primary care provider. Hysterectomy status will also be reviewed with participants on *Form 10 - HRT Management and Safety Interview* at each contact.

If the reason is <u>not</u> for cancer, restart study pills when the primary care provider feels that it is safe. All women who undergo a hysterectomy should be issued a new bottle of study pills. This will also ensure that the participant is on the correct study pill for her new hysterectomy status. This change will not require unblinding. Clinical Center staff *must call the CCC Data Coordinator for identification of the new bottle*.

Note that women, who undergo an endometrial ablation but keep their uterus, may continue in their original study arm.

5.5.2 Health Problems Requiring Serious Review

The following should be considered as major adverse effects that will prompt a *serious review* of the need to temporarily or completely stop study pills. (Please consult with your PI and/or Consulting Gynecologist):

- **Symptomatic or active gall bladder disease:** Presence of right upper quadrant pain, nausea, anorexia, or jaundice; liver enzyme abnormalities; or ultrasound-diagnosed cholelithiasis. If a participant has had a cholecystectomy, study pills do not need to be stopped. The decision about continuing study pills should be based on clinical discretion with input from the participant's health care provider.

- **Acute pancreatitis**: Presence of upper abdominal pain, nausea, vomiting, sweating, tachycardia, cyanosis, or elevated serum amylase or lipase.
- **Any hospitalization**
- **Surgery requiring short-term prophylactic anticoagulant therapy** (anticoagulants being used to treat thrombophlebitic events require HRT termination).
- **Hysterectomy for a non-cancerous condition** (See *Section 5.5.1 – Management of HRT after a Hysterectomy for a Non-Cancerous Condition).*

If it is necessary to temporarily stop study pills, follow procedure in *Section 5.5.3 – Health Problems That Require Temporary Discontinuation.*

5.5.3 Health Problems That Require Temporary Discontinuation

The following adverse experiences will result in the temporary discontinuation of the hormone replacement therapy:

- Myocardial infarction
- Stroke
- Surgery involving the use of general or spinal anesthesia. (If a participant is scheduled for surgery, she should be advised to speak with her surgeon to see if she should stop study pills ahead of time.)
- Any illness or injury that results in immobilization requiring strict bed rest for more than one week
- Any severe illness in which HRT is temporarily inappropriate (including newly diagnosed TIAs, retinal vascular thrombosis, or other cardiovascular conditions that may increase a participant's risk for a thrombotic event).

If a participant needs to temporarily discontinue her study pills, complete *Form 54 - Change of Medications* to indicate she has stopped. You do not need to collect her bottle until the next regularly scheduled visit. Maintain contact with the participant and her attending primary care provider to determine if and when she can return to her study medicines. When she is able to restart her pills, she can continue using the same bottle. Complete *Form 54* again to indicate she has restarted. Follow procedures in *Section 5.5.1 – Management of HRT After Hysterectomy for Non-Cancerous Condition* if the participant has a hysterectomy. Depending on the length of time she is off study pills, a *Form 7 - Participation Status* may need to be completed. Refer to *Section 16 - Follow-Up*.

5.5.4 Health Problems Requiring HRT Termination

The following adverse experiences will require permanently stopping HRT medications and recording that action on *Form 7 - Participation Status*. For each of these adverse conditions, documentation will be required before the final decision to permanently stop the medication is made. Documentation can include pathology reports, reports of other diagnostic or surgical procedures, or primary care provider or hospital records.

(Note: deleting meningioma from this list was approved by the Steering Committee in June 2000.)

- Deep vein thrombosis (DVT)
- Pulmonary embolus (PE)
- Starting anticoagulant medications for thrombophlebitic events.
- Endometrial hyperplasia with atypia (see *Section 5.1.2.4 – Exclusions Based On Baseline Endometrial Evaluation.*).
- Starting on estrogen, progesterone, testosterone, or Tamoxifen or other SERMS (those preparations that act systemically, such as pills, shots, transdermal patches and skin implants). If a participant subsequently discontinues use of such preparations, you may restart her on HRT study pills. HRT

participants may continue to take WHI HRT study pills while they are using prescribed estrogen, progesterone, or testosterone creams; estrogen suppositories (e.g., VagiFem™); Estring™ (a vaginal estrogen delivery system); or over-the-counter (e.g., herbal) hormone preparations.

- Malignant melanoma
- Endometrial cancer
- Breast cancer including intraductal carcinoma on biopsy or carcinoma in-situ
- Triglycerides above 1,000 mg/dl

Note that participants who require long term corticosteroid therapy after randomization may continue their study pills. However, CPs should encourage participants to discuss additional treatment for prevention of osteoporosis with their own primary care providers.

For endometrial biopsy findings, discontinuation of study treatment should be as follows:

- If findings of simple or complex (adenomatous) hyperplasia persist after appropriate management as outlined in *Section 5.4.3.2 – Management According to Endometrial Histology*, discontinue the medications permanently (complete *Form 7 – Participation Status*). Refer the participant to her primary care provider for evaluation and treatment and mail or fax copies of all pertinent reports to them.
- If a participant has a hysterectomy as part of her treatment, see *Section 5.5.1 – Management of HRT After Hysterectomy for Non-Cancerous Condition* for the necessary steps to restart her study pills. (Complete *Form 7* or *Form 54 – Change in Medications* (as appropriate) again to indicate she is restarting the intervention and dispense a new bottle of study pills.)
- If pathologic findings (on either local or central pathology reading) are atypia or endometrial cancer, permanently discontinue HRT medications, complete *Form 7 - Participation Status*, and refer the participant to her primary care provider for evaluation and management. Notification of the participant and her primary care provider should be done by the CC physician or CP. Mail or fax copies of all pertinent reports to the primary care provider.

For pelvic exam and Pap smear findings, see *Volume 2, Section 9.9.2 – Performing the Pelvic Exam and Pap Smear* and *Section 9.9.3 – Pelvic Exam and Pap Smear Findings*.

5.5.5 Other Issues Requiring Discontinuation of HRT Study Pills

In the event that a participant refuses required routine safety examinations and/or diagnostic follow-up exams for suspicious findings, study pills may need to be discontinued (either temporarily or permanently).

Participants are required to have safety exams completed at specific intervals to stay on study pills. These tasks include CBE, pelvic, Pap smear, and *Form 10* completion. See *Table 16.2- Follow-up Clinical Examinations/Minimum Requirements for HRT Participants* for detailed instruction.

Study pills may be restarted if the participant has the routine exam and/or recommended diagnostic follow-up exams and any abnormal findings are cleared. Complete *Form 54 – Change of Medications* when stopping or resuming study pills.

5.5.6 Guidelines for Restarting a HRT Participant Who Discontinued Pills for 12 Months or More

In the event that a participant chooses to restart her HRT study pills after discontinuing her pills for 12 months or more (and it is appropriate to do so), the following procedures are required to be completed and reviewed before study pills can be dispensed.

- Mammogram (*Form 85*) **must be completed within last 12 months.**
- Clinical Breast Exam (*Form 84*) **must be completed within last 12 months.**
- Pelvic Exam (*Form 81*) **must be completed within last 12 months.**
- Pap Smear (*Form 92)* **must be completed within last 3 years.**

- *HRT Management and Safety Interview (Form 10)* **must be completed at the time of the restart.**

All examinations must be considered normal. An endometrial aspiration is **not required** to restart a participant unless there was abnormal bleeding since the intervention was stopped. It is also advised to seek approval and support of the participant's PCP if her intervention was stopped primarily for medical reasons.

5.5.7 Guidelines for Restarting HRT Study Pills for a Participant Who Has Had a MI or Stroke

CC staff should not actively encourage participants to restart study pills after a new diagnosis of TIA, MI, stroke, or other cardiovascular condition that can increase a participant's risk for a thrombotic event. If the participant wishes to restart (or continue) study pills, advise her to discuss with her primary care provider the advisability of restarting study pills that may contain estrogen. If the participant prefers, she may ask a representative of the CC to discuss this question with her provider. If the participant still wishes to restart (or continue) study pills, and the CC PI approves, the participant may resume her pills.

5.6 Unblinding (Required)

All CC personnel and participants will be blinded to individual participant HRT treatment assignments. All efforts will be made to prevent unblinding of participants for the duration of the trial. However, in some instances of unexpected or abnormal bleeding, it may be necessary for a CC consulting gynecologist or a private primary care provider to be unblinded to ensure maximal participant safety.

Each CC must identify an unblinding officer who will have access to the database function for unblinding. This is usually the CC Data Coordinator. Only the CC consulting gynecologist may be unblinded through the unblinding officer. The unblinding officer may not be involved in clinical activities or the adjudication of outcomes. Unblinding information is restricted to the CC consulting gynecologist and the unblinding officer. The CC consulting gynecologist, however, should be the only person who keeps a record of the participant's treatment arm. Any other documents (e.g., log or participant progress notes) should only include the fact that an unblinding occurred. As long as the unblinded information is limited to these individuals and these persons are not involved in outcome adjudication, the potential for biasing study outcomes is minimal. Bias can further be minimized by maintaining participant blinding, even when unblinding of the gynecologist becomes necessary. Serious complications such as those requiring surgery may necessitate unblinding a small number of participants.

Depending on the clinical findings, unblinding will be considered under circumstances involving either participant safety or management of adverse effects. Such conditions are discussed in *Section 5.4.3 – Management of Vaginal Bleeding.* Should unblinding become necessary, the unblinding officer will execute the database function, which will require input of data (from the CP or CC consulting gynecologist) regarding rationale for unblinding. (See *Vol. 5 - Data System, Section 6.3 – Unblinding Procedures.*)

5.7 Follow-Up Endometrial Biopsies

HRT participants with a uterus may have a follow-up endometrial biopsy to investigate reasons for bleeding while on study pills, or because they have been identified as a participant in the 6% endometrial aspiration subsample done in years 3, 6, and 9.

WHILMA report *Members in Subsample* (*WHIP 1410*) will identify participants in the endometrial aspiration subsample eighteen months before the biopsy is required. CCs should inform participants of the need for this task as soon as the participant is identified. All attempts should be made to obtain a biopsy sample. If entry is not possible, or the participant refuses, obtain a transvaginal uterine ultrasound instead. If the participant refuses the ultrasound, there is no effect on her status in the HRT.

Follow-up biopsies should be sent to local pathologists for evaluation (see *Section. 5.7.1 – Reading of Follow-Up Biopsies*). If abnormal results are identified in either the follow-up of abnormal bleeding or in the subsample pathology report, follow the treatment guidelines in *Section 5.4.3.2—Management According to Endometrial Histology*.

5.7.1 Reading of Follow-Up Endometrial Biopsies

Thorough education and establishment of lines of communication with CC staff (including the CC consulting gynecologists), primary care providers and local pathologists will assure effective, appropriate, and timely care of WHI participants. Send your local pathologist the following WHI Endometrial Histology Classification to aid in their reporting of results. Classifications include:

- No endometrial tissue identified
- Insufficient specimen
- Normal atrophic endometrium
- Normal secretory endometrium
- Normal proliferative endometrium
- Cystic (simple) hyperplasia present
- Cystic (simple) hyperplasia with atypia
- Adenomatous (complex) hyperplasia present
- Adenomatous (complex) hyperplasia with atypia
- Atypia present (carcinoma in-situ [CIS])
- Cancer present
- Other (include description)

The clinical management of women will be based on local pathology readings. There are some general principles that guide management decisions:

- The randomized woman is first a patient and second a participant in the WHI.
- The randomized woman’s primary care provider must have the latitude to act ”in the best interest” of the participant.

The local pathologist’s reading will be sent to the participant’s respective CC, which if necessary, will then forward the readings to the primary care provider in a timely fashion.

Section 5
Hormone Replacement Trial

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SECTION 6

DIETARY MODIFICATION (DM)

INTRODUCTION

The objective of the Dietary Modification (DM) component of the Clinical Trial (CT) is to determine the effect of a low-fat dietary pattern that includes five or more daily servings of fruits and vegetables and six or more daily servings of grains on reducing the incidence of breast cancer, colorectal cancer, and coronary heart disease.

The proposed study will at the same time provide information on the effect of a low-fat dietary pattern on serum cholesterol, blood pressure, and body weight. If a low-fat diet does reduce the incidence of any one of the clinical outcomes of breast cancer, colorectal cancer, or coronary disease, the public health implications will be enormously important.

The participants in the DM component of the CT will be randomized into one of two arms: Comparison (Control) or Dietary Change (Intervention). The preferred terminology is Comparison or Dietary Change when interacting with participants. The terms Control (Comparison) and Intervention (Dietary Change) are interspersed throughout the WHI Manuals, recognizing that the documents are limited to staff and investigator use.

6.1 Assessment of DM Eligibility Issues (Required)

The following topics should be considered before a participant is randomized into the DM.

6.1.1 Food Frequency Questionnaire (Required)

All participants complete *Form 60 - Food Frequency Questionnaire* (*FFQ)* to screen out potential DM participants who are already consuming dietary intakes of less than 32% calories from fat.

Women are ineligible for DM if their baseline *FFQ* nutrient analysis is (1) less than 32% energy from fat, or (2) less than 600 kcalories, or (3) more than 5,000 kcalories.

6.1.2 Low Fiber (Required)

During the initial screening, the low-fiber/low-residue question on *Form 2/3 - Eligibility Screen* is meant to identify participants who are following physician prescribed dietary restrictions that may be incompatible with the increased fruits, vegetables and grains of the DM Intervention program.

If a participant responds "yes" to the question on *Form 2/3 - Eligibility Screen* that she is following a physician prescribed low-fiber diet, she would be temporarily ineligible for DM. Clinical Centers (CC) may determine when to rescreen using the procedures described in *Section 4.5.4 - Rescreening Ineligible Participants*. However, before starting the rescreening process, a Nutritionist should assess the frequency, severity, and duration of the episodes where a low-fiber diet is prescribed, and use clinical judgment to determine how this would impact on the woman's ability to follow the DM Intervention program. If the nutritionist finds that the woman would not be a good DM candidate based on these considerations, use the staff assessment question on *Form 6 - Final Eligibility Assessment* to make the woman ineligible.

6.1.3 BMI (Required)

Participants who have a BMI < 18 are not eligible for DM unless the Nutritionist overrides the exclusion on *Form 6 - Final Eligibility Assessment*. If a participant is joining HRT+DM, the Clinic Practitioner's decision to override the BMI criterion (or not override the criterion) for HRT does not affect the Nutritionist's override decision for DM.

6.1.4 Number of Meals Prepared Away From Home (Required)

Participants who eat 10 or more meals each week prepared away from home are not eligible for DM unless the CC Nutritionist overrides this exclusion. For a definition of a meal prepared away from home, refer to the Item Instructions for meals away from home question on *Form 2/3 - Eligibility Screen,* Item Instructions.

Before overriding the meals away from home exclusion criterion, the Nutritionist should refer to *Form 6 - Final Eligibility Assessment,* Item Instructions and consider the following:

- **Study goals.** The Nutritionist should assess a participant's ability to comply with the rigorous dietary changes required by the DM Intervention. A woman who eats 10 or more meals prepared away from home each week may have difficulty reducing her fat intake to the level required for the study.
- **Lifestyle.** The Nutritionist should assess if a participant's lifestyle is compatible with the demands of the DM Intervention. Frequent meals prepared away from home may indicate a lifestyle that is too complicated or busy to accommodate the time commitment required for successful participation and performance.

6.1.5 Availability During Next Year (Required)

Women who are interested in DM participation must be available for the first six months of DM Intervention (i.e., Sessions 1-12). Currently, there are no provisions for women to "drop-in" to DM Intervention group sessions at other CCs. Therefore, CCs should try to identify potential DM participants who travel away from their home for extended periods of time, as soon as possible in the screening process.

To assure that a randomized DM Intervention participant will be available for the first six months of DM Intervention meetings, *Form 2/3 - Eligibility Screen,* gathers information about a participant's availability for one year from the time she completes the form. If a woman responds "no" to being available for the next year, she is considered "not interested in DM at this time." A participant may reinitiate the screening process when she is available.

6.1.6 DM Eligibility Checklist (Required)

At the SV3 before randomization, the certified Lead Nutritionist or a staff person certified to administer the *DM Eligibility Checklist* assesses the participant's willingness and ability to complete the activities of the DM Intervention using the *DM Eligibility Checklist* (see *Figures 6.1a and 6.1b*). This review takes about 30 minutes and requires judgment by the staff who administer the Checklist.

The *DM Eligibility Checklist* provides a discussion guideline for assessing key eligibility issues related to the following topics:

- DM Adherence
- DM Design
- DM Expectations
- DM Randomization

The topics listed on the *DM Eligibility Checklist* are the minimum points to cover. The points may be addressed in any order; however, WHI experience to date suggests that the order shown in *Figures 6.1a and 6.1.b* works well.

The participant must satisfactorily complete the *DM Eligibility Checklist* review process, including the completion of an acceptable 4DFR, before she is eligible for DM. DM eligibility is assessed at several points during the *DM Eligibility Checklist* review process. If the participant becomes ineligible during the *DM Eligibility Checklist* review process, the review is stopped and staff document the participant's eligibility status on one of the following three forms: *Form 11 - Consent Status, Form 6 - Final Eligibility Assessment,* or *Form 62 -4DFR*. The form used depends on the reason for ineligibility as described in *Sections 6.1.6.1 - Review DM Adherence Related Issues, 6.1.6.3 - Review DM Expectations, and 6.1.6.4 - Review DM Randomization.*

6.1.6.1 Review DM Adherence Related Issues (Required)

The following adherence related areas are to be considered when determining eligibility for the DM: (1) weight loss as a motivator for joining DM, (2) history of weight cycling, (3) unusual eating patterns, and (4) the ability to complete 4DFRs in order that adherence can be monitored.

Begin the interview by reviewing the participant's motivation for joining the DM. Refer to *Figure 6.1-b - DM Eligibility Checklist with Questions* for examples of open-ended questions to ask the participant.

Weight Loss as Motivator for Joining DM

Carefully assess and evaluate the appropriateness of a woman who is interested in losing weight or actively and intentionally losing weight as evidenced by (1) using weight loss medications (prescription or over-the-counter), (2) considering the use of weight loss medications (prescription or over-the-counter), (3) on a weight loss program, (4) considering a weight loss program, and (5) stating an interest in losing weight.

A woman stating that weight loss is a motivator for joining DM is not a good candidate for DM. She may have unrealistic expectations for DM that could cause disappointment and later result in her dropping from the study. Clarify that the DM program is not a weight loss program. Remind the participant that DM group sessions will not include information on weight loss methods. Ask the participant open-ended questions to assess her feelings about weight loss. Ask the participant how she would feel if she didn't lose weight or if she gained weight.

In addition, some women may be following a weight loss regimen that conflicts with the DM Intervention goals. Look for potential dietary conflicts when reviewing the *4DFR* for unusual eating patterns.

Further, a woman interested in losing weight may be hoping to be randomized to the Dietary Change group and will likely be disappointed if she's randomized to the Comparison group. Look for women who are unwilling to be randomized to either DM group when reviewing DM randomization.

History of Weight Cycling

A woman exhibiting a history of weight cycling may not be an appropriate candidate for the DM. Repetitive weight loss and weight gain during adulthood may make it more difficult for the participant to make permanent lifestyle changes required by the DM Intervention. The nutritionist should evaluate if the woman's weight history will negatively impact her performance in the DM if she is randomized to the Dietary Change group. Refer to *Form 34 — Personal Habits Questionnaire*, Question 4.

Determine Eligibility

- If the participant's primary motivation for joining the study is weight loss and she declines further screening to participate in DM, stop the *DM Eligibility Checklist* review process. Thank her for her interest. Complete *Form 11 - Consent Status*. Mark all reasons that apply.
- If the Group Nutritionist or Dietary Assessment staff feel that the participant's primary motivation for joining the study is weight loss or her weight history will negatively impact her performance, stop the *DM Eligibility Checklist* review process. Explain that she is ineligible for the study. Thank her for her interest. Complete the Staff Impression for DM question on *Form 6 - Final Eligibility Assessment*. Mark the "ineligible" box and enter staff ID code. Record the reason as "focus on weight loss" or "weight history" as applicable.
- If the participant is not focused on weight loss as a motivation for joining the WHI or does not have a weight history that contraindicates randomization, continue with the *DM Eligibility Checklist* review process.

Review the *4DFR* for Unusual Eating Patterns

Visually scan each page of the *4DFR* for unusual eating patterns. This is a judgment decision. The purpose of this review is to identify participants whose eating patterns appear incompatible with the DM Intervention goals. Look for participants who appear to have compulsive eating patterns, skip meals or avoid entire food groups, particularly fruits, vegetables, or grains. In addition, look for participants who have unique or very limited intakes of foods (e.g., liquid diets, routine consumption of diet beverages, bars etc. or fasting regimens). If a participant eats a limited variety of foods, ask open-ended questions to assess whether the four days recorded are typical and whether she is willing and able to include more variety in her diet. *See Figure 6.1-b DM Eligibility Checklist* with *Questions* for examples of open-ended questions.

Determine Eligibility

- If the participant feels that she is not willing or able to choose foods that are compatible with the DM Intervention goals and declines further screening to participate in DM, stop the *DM Eligibility Checklist* review process. Thank her for her interest. Complete *Form 11 - Consent Status*. Mark all reasons that apply.
- If the Group Nutritionist or Dietary Assessment staff feel that the participant has eating patterns or food choices that would **not** be compatible with the DM Intervention goals, stop the *DM Eligibility Checklist* review process. Explain that she is ineligible for the study. Thank her for her interest. Complete the Staff Impression for DM question on *Form 6 - Final Eligibility Assessment*. Mark the "ineligible" box and enter staff ID code. Record the reason as "unusual eating patterns."

- If the Group Nutritionist or Dietary Assessment staff feel that the participant has eating patterns or food choices that are compatible with the DM Intervention goals, continue the *DM Eligibility Checklist* review process.

Review the *4DFR* for Completeness

Evaluate the 4DFR for sufficient vision, reading and writing skills to determine a woman's future ability to self-monitor (i.e., record and calculate fat, fruit/vegetable, and grain scores), complete forms and complete make-up assignments.

The *4DFR* is considered to be "not satisfactorily completed" if any of the following items are inadequate:

- **A minimum of three days are required.** The *4DFR* with three days is acceptable. However, if fewer than three days are recorded, randomization should be delayed until the participant completes an acceptable *4DFR* (see *Section 10.1.6 - Common Problems and Solutions*).
- **Food record is legible.** Determine the participant's willingness and ability to provide legible records of the food she eats. Look for whether the participant can write well enough to keep self-monitoring tools if she is randomized into the Dietary Change group.
- **Food descriptions are complete.** Determine the participant's willingness and ability to completely describe the food she eats. Look for whether the participant can describe foods with enough detail to keep self-monitoring tools if she is randomized into the Dietary Change group. Select one or two different food items (e.g., main dishes, side dishes, desserts) on each page. Briefly review how the participant described the foods. Use the examples provided in the *4DFR* (pages 6, 8, and 10) as a guideline. Refer to *Figure 6.1-b - DM Eligibility Checklist with Questions* for examples of open-ended questions to ask the participant.
- **Serving sizes are reasonably estimated.** Determine the participant's willingness and ability to reasonably estimate portion sizes. Briefly review the portion sizes listed in the record. Look for unreasonable estimates (e.g., a 7" diameter orange or a 1 oz. chicken leg). Refer to *Figure 6.1-b - DM Eligibility Checklist with Questions* for examples of open-ended questions to ask the participant.

The CC Lead or Group Nutritionist should be involved in deciding whether a woman is an appropriate candidate for DM if she cannot read or write English (or Spanish) well. Dietary Change participants must be able to read and write English (or Spanish) well enough to complete the self-monitoring and home activities that are part of the intervention. Dietary Change group sessions use a discussion format and, therefore, rely more heavily on verbal skills than reading and writing skills. Dietary Change makeup sessions, on the other hand, rely more heavily on reading and writing skills because the participant is expected to read session materials and complete session worksheets before meeting with the nutritionist to review the missed session. Refer to *Vol. 2 - Procedures, Section 20.2.7 - Women with Special Needs.*

Determine Eligibility

- If a participant has not satisfactorily completed the *4DFR*, stop the *DM Eligibility Checklist* review process. Explain that she is ineligible for the study. Thank her for her interest. Complete the appropriate questions in the *4DFR* data entry box (shaded section on back page) using *Vol. 3 - Forms, 4DFR* General and Item Instructions. Mark "no" to the *4DFR* satisfactorily completed question. Forward the *4DFR* to data entry.
- If a participant has satisfactorily completed the *4DFR*, complete the appropriate questions in the *4DFR* data entry box (shaded section on back page) using *Vol. 3 - Forms, 4DFR* General and Item Instructions. Mark "yes" to the *4DFR* satisfactorily completed question. Continue the *DM Eligibility Checklist* review process.

Assess Willingness and Ability to Self-Monitor

Explain that self-monitoring is a critical part of the study. Review the frequency of self-monitoring for the Dietary Change group. Ask open-ended questions to assess the participant's willingness to record the foods she eats for each group session for the duration of the study. See *Figure 6.1-b - DM Eligibility Checklist with Questions* for examples of open-ended questions to ask participants.

Determine Eligibility

- If the participant feels that she is not willing or able to self-monitor and declines further screening to participate in DM, stop the *DM Eligibility Checklist* review process. Explain that she is ineligible for the study. Thank her for her interest. Complete *Form 11 - Consent Status*. Mark all reasons that apply.
- If the Group Nutritionist or Dietary Assessment staff feel that the participant is unwilling or unable to self-monitor, stop the *DM Eligibility Checklist* review process. Explain to the participant that she is ineligible for the study. Thank her for her interest. Complete the Staff Impression for DM question on *Form 6 - Final Eligibility Assessment*. Mark the "ineligible" box and enter staff ID code. Record the reason as "unwilling or unable to self-monitor."
- If the Group Nutritionist or Dietary Assessment staff feel that the participant is willing and able to self-monitor, continue the *DM Eligibility Checklist* review process.

6.1.6.2 Review DM Design (Required)

Briefly review the DM design. The purpose of this review is to assess the participant's understanding that the DM has two groups (Comparison and Dietary Change) and that both groups are equally important for the success of the study.

Define both DM groups. Briefly explain that the DM study has two different groups. The Comparison group will eat as they usually do. The Dietary Change group will meet with a Nutritionist and other participants to learn how to eat less fat and more fruits, vegetables, and grains.

Reinforce the importance of both groups. Briefly explain that both groups are important for the success of the study. The study needs to have a group of people who do not change the way they eat in order to see if changing diet makes any difference. There could be no comparison without these two groups. See *Figure 6.1-b - DM Eligibility Checklist with Questions* for examples of open-ended questions to ask participants.

6.1.6.3 Review DM Expectations (Required)

Briefly review the expectations of the two groups (Comparison and Dietary Change). The purpose of this review is to assess the participant's ability and willingness to meet the requirements of either group. Include the following information:

Review General DM Expectations

- **Review semi-annual contact.** Let the participant know that she will be contacted by a CC staff person (by phone, mail, or in-person depending on your CC procedures) every six months to check on general health and update any changes in address or phone numbers.
- **Review annual follow-up visit.** Let the participant know that she will be asked to come back to the CC once a year for a follow-up visit. The procedures done at this visit are similar to the baseline screening procedures (height, weight, blood draws, completion of forms, etc.).
- **Review dietary assessment requirements.** Let the participant know that she may be asked to occasionally provide information on the foods that she eats (*FFQ*, potential *4DFR* and/or 24-Hour Recall).

Review Comparison Group Expectations

Rather than repeating information given at previous screening visits, ask the participant to describe her understanding of the Comparison group expectations. If the participant is unclear about the expectations, clarify with the following information:

- **Eat as you normally do.** Briefly explain that a participant in the Comparison group will not be asked to make any changes in her eating patterns. She will continue to eat the way she normally eats. She will not meet with a Nutritionist. She will be followed for health outcomes in the same way as the Dietary Change group women.

Ask the participant open-ended questions to assess her understanding, willingness, and ability to meet DM Comparison group expectations. See *Figure 6.1-b - DM Eligibility Checklist with Questions* for examples of open-ended questions.

Review Dietary Change Group Expectations

Rather than repeating information given at previous screening visits, ask the participant to describe her understanding of the Dietary Change group expectations. If the participant is unclear about the expectations, clarify with the following information:

- **Review dietary changes.** Briefly explain that a participant in the Dietary Change group will be taught how to lower the fat in her diet and increase her servings of fruits, vegetables, and grains. Explain that the dietary program is not meant to be a weight loss program. The changes she will be asked to make are lifestyle changes that she will be expected to maintain for 8-12 years. Ask open-ended questions to assess her willingness and ability to make dietary changes. In addition, ask open-ended questions to assess how her family will react to her involvement in the dietary change program.

- **Review expectations of group sessions.** Briefly explain that during the first year, group meetings are held once a week for six weeks, once every two weeks for six weeks, and once a month for nine months. After the first year, the group sessions are four times a year until the study ends. Each group session lasts about two hours.

- **Determine participant's availability to attend group sessions.** Pay close attention to a participant's response to the following areas:

  a. Does the woman have a flexible schedule (i.e., more than one day of the week, or time of the day, that she is available to attend group sessions)?

  b. Will the woman be available to attend all group sessions, especially during the first year when group sessions are more frequent?

  c. Does the woman travel for extended periods of time (business or retirement trips)?

  d. Does the woman have reliable transportation to the CC? Will weather (or darkness) impact the woman's transportation? Does the woman live a distance from the CC and is she willing to come for all group sessions despite living far from the clinic?

- **Determine participant's willingness to attend group sessions.** Explain that group sessions are very important to help the participant learn how to change. She must be willing to attend all sessions. If she misses a session, she will be expected to make it up. Ask open-ended questions to assess the participant's willingness to attend sessions and to make-up missed sessions.

Ask the participant open-ended questions to assess her understanding, willingness, and ability to meet DM Dietary Change group expectations. See *Figure 6.1-b - DM Eligibility Checklist with Questions* for examples of open-ended questions to ask participants.

Determine Eligibility

- If the participant is unwilling or unable to meet DM expectations for the Comparison or the Dietary Change group and declines further screening to participate in DM, stop the *DM Eligibility Checklist* review process. Thank her for her interest. Complete *Form 11 - Consent Status*. Mark all reasons that apply.

- If the Group Nutritionist or Dietary Assessment staff feel that the participant is unwilling or unable to meet the DM expectations, stop the *DM Eligibility Checklist* review process. Explain that the participant is ineligible for DM. Thank her for her interest. Complete the Staff Impression for DM question on *Form 6 - Final Eligibility Assessment*. Mark the "ineligible" box and enter staff ID code. Record the reason as "unwilling (or unable) to meet DM expectations."

- If the participant is willing and able to meet the expectations of both groups, continue with the *DM Eligibility Checklist* review process.

6.1.6.4 Review DM Randomization (Required)

Determine Participant's Willingness to be Randomized in Either Group (Comparison or Dietary Change)

Ask the woman an open-ended question to assess her willingness to be in either group. For example, ask the participant how she feels about not knowing the group she will be assigned to. See *Figure 6.1-b - DM Eligibility Checklist with Questions* for examples of open-ended questions to ask participants.

Determine Eligibility

- If the participant is unwilling to be randomized into either group and declines further screening to participate in DM, stop the *DM Eligibility Checklist* review process. Thank her for her interest. Complete *Form 11 - Consent Status*. Mark all reasons that apply.
- If the Group Nutritionist or Dietary Assessment staff feel that the participant is not willing to be randomized into either group, stop the *DM Eligibility Checklist* review process. Explain that she is ineligible for the study. Thank her for her interest. Complete the Staff Impression for DM question on *Form 6 - Final Eligibility Assessment*. Mark the "ineligible" box and enter staff ID code. Record the reason as "unwilling to be randomized."
- If the participant is willing to be randomized to either group, forward the *4DFR* to data entry. Inform the CC staff responsible for randomization that the participant is ready to be randomized.

6.2 Randomize DM Participant (Required)

Participants Eligible for DM

Participants who satisfactorily complete the *DM Eligibility Checklist* review process should be randomized using the procedures outlined in *Section 4 - Screening* and *Section 4.6.3.2 - DM Randomization.* The CC should have local procedures in place to maintain blinding of the Dietary Assessment staff to the participant's randomization assignment.

At randomization, if the participant's *4DFR* is identified as part of the *4DFR* subsample, follow the procedures in *Section 10 - Dietary Assessment.* If the *4DFR* is not identified in the *4DFR* subsample, no further documentation of the *4DFR* is required. File the completed *4DFR* at the CC.

Participants Ineligible for DM

Participants who do not satisfactorily complete the *DM Eligibility Checklist* review process should not be randomized. File the *4DFRs* for an ineligible participant in her file at the CC.

Figure 6.1a
DM Eligibility Checklist

Review DM Adherence Related Issues

_____ Review motivation for joining DM. Clarify that DM is not a weight loss program

_____ Review history of weight cycling

_____ Review *4DFR* for unusual eating patterns, estimate daily servings of fruit/veg and grains

_____ Review the *4DFR* to assess satisfactory completion:

- A minimum of three days is required (four days is ideal)
- Food record is legible
- Food descriptions complete and serving sizes reasonably estimated

_____ Assess willingness and ability to self-monitor

Review DM Design

_____ Review the general DM design; include the following:

- Definition of the two DM groups (Comparison and Dietary Change groups)
- Reinforce the importance of both groups to the study

Review DM Expectations

_____ Review general DM expectations; include the following:

- Semi-annual contact (via phone, mail, or in person)
- Annual follow-up visits with procedures similar to baseline (height, weight, blood pressure, blood draws, etc.)
- Dietary assessment requirements: occasional record-keeping of foods you eat (occasional *FFQ*, potential *4DFR* and/or 24-Hour Recall)

_____ Review **Comparison group** expectations; include the following:

- Eat what you normally do, no changes required

_____ Review **Dietary Change group** expectations; include the following:

- Change eating patterns to greatly reduce fat and increase fruits/vegetables and grains
- Review group session schedule and length of group sessions
- Determine availability to attend group sessions
  - — Flexibility when available to attend groups
  - — Availability during first year of DM Intervention
  - — Extended periods of travel (business or retirement)
  - — Transportation available and distance to travel to CC
- Determine willingness to attend sessions
  - — Willingness to make-up missed group sessions

Review DM Randomization

_____ Determine the participant's willingness to be randomized into either group

Figure 6.1b
DM Eligibility Checklist with Questions

Review DM Adherence Related Issues

_____ Review motivation for joining DM. Clarify that DM is not a weight loss program

What interests you in the DM study? What is your motivation for joining the WHI?

Do you understand that the Dietary program is not a weight loss program? How do you feel about that?

_____ Review history of weight cycling

How often are you dieting?

Are you currently dieting or thinking about dieting? How much weight are you trying to lose?

Have you tried to lose weight before? What methods have you used to lose weight? Were you successful in losing weight? How much weight did you lose? Were you successful in maintaining the weight loss?

_____ Review *4DFR* for unusual eating patterns, estimate daily servings of fruit/veg and grains

How does the amount and type of food you ate compare to what you usually eat?

It looks like you ate about ___servings of F/V, how does that compare to what you usually eat? If low ask: *What would it be like for you to eat more fruits and vegetables? Are there any fruits and vegetables you don't eat? Which ones? Can you tell me why you don't eat these?*

It looks like you ate about ___ servings of grains, how does that compare to what you usually eat? If low ask: *What would it be like for you to eat more grains? Are there any grains you don't eat? Which ones? Can you tell me why you don't eat these?*

_____ Review the *4DFR* to assess satisfactory completion:

- A minimum of three days is required (four days is ideal)
- Food record is legible
- Food descriptions complete and serving sizes reasonably estimated

Can you tell me more about how this [food name] was prepared?

How did you estimate the amount of this [food name] you ate?

When did you record the foods you ate?

_____ Assess willingness and ability to self-monitor

Tell me about how keeping a food record might have influenced what you ate.

How did you feel about keeping a food record?

What would it be like for you to keep track of the foods you eat on a regular basis? For a long time?

What kinds of things might come up that would keep you from keeping track of what you eat?

What concerns, if any, do you have about recording what you eat on a regular basis?

Review DM Design

_____ Review the general DM design; include the following:

- Definition of the two DM groups (Comparison and Dietary Change groups)
- Reinforce the importance of both groups to the study

Why do you think the Comparison group is important for the study?

Review DM Expectations

_____ Review general DM expectations; include the following:

- Semi-annual contact (via phone, mail, or in person)
- Annual follow-up visits with procedures similar to baseline (height, weight, blood pressure, blood draws, etc.)
- Dietary assessment requirements: occasional record-keeping of foods you eat (occasional *FFQ*, potential *4DFR* and/or 24-Hour Recall)

_____ Review **Comparison group** expectations; include the following:

- Eat what you normally do, no changes required

What is your expectation of what you would be asked to do if randomized to the Comparison group?

_____ Review **Dietary Change group** expectations; include the following:

- Change eating patterns to greatly reduce fat and increase fruits/vegetables and grains

What is your expectation of what you would be asked to do if you were randomized to the Dietary Change group?

How would you feel about changing your eating patterns to eat less fat?

How would you feel about increasing your intake of fruits and vegetables?

How would you feel about increasing your intake of grains?

What might interfere with you changing your eating habits?

How would your family react to you changing your eating habits?

- Review group session schedule and length of group sessions
- Determine availability to attend group sessions
  - — Flexibility when available to attend groups

    How will a "fixed" meeting date fit into your current schedule?

    How much control do you have over your daily schedule?

  - — Availability during first year of DM Intervention

    Are you anticipating a change in your availability to attend sessions during the next year?(e.g. change in work schedule, new job, retirement, babysitting responsibilities)?

  - — Extended periods of travel (business or retirement)

    How often do you travel for business or pleasure? When you travel how long do you usually stay?

  - — Transportation available and distance to travel to CC

    What has been your experience getting to the CC for your screening visits?

    What types of situations could make it difficult for you to get to the CC (e.g. weather, night driving, reliable transportation, etc.)?

    Do you have any concerns about commuting to the CC for group sessions?
- Determine willingness to attend sessions
  - — Willingness to make-up missed group sessions

    What kinds of things might come up that would keep you from attending a group session?

    What would it be like for you to work a make-up session into you schedule, if you miss group sessions?

    How would you feel about doing session activities (like shopping, worksheets, keeping track of what you eat, etc.) in addition to the time you spend in the group session?

Review DM Randomization

_____ Determine the participant's willingness to be randomized into either group

How do you feel about not knowing which group you will be randomized into?

How would you feel if you were randomized to the Comparison group?

How would you feel if you were randomized into the Dietary Change group?

6.3 Handling Randomized DM Participants (Required)

Make sure randomized DM participants leave with all the materials handed out by the CC at randomization (see *Section 4.3.5.2 - Participant Hand-Outs*).

6.3.1 Participants Assigned to the DM Comparison Group (Required)

Participants randomized to the DM Comparison arm meet with a non-blinded staff person to review the requirements of the Comparison group and its importance in the DM Trial. The general strategy for women randomized into the Comparison group is one of minimum interference with their customary diets while collecting nutritional and health outcome data appropriate for comparison with the Dietary Change group.

Health and Dietary Information

Give DM Comparison group participants a copy of the USDA/DHHS Dietary Guidelines for Americans (3rd edition) in addition to the other materials handed out at randomization. Restrict dietary responses to provide only information on the various food groups and the Recommended Dietary Allowances (RDAs). DM Comparison group participants must not be given any additional nutrition information, counseling, or resources such as health pamphlets with nutritional advice, the American Dietetic Association Consumer Information phone numbers, etc. For a list of health information brochures that can be used with DM Comparison participants as retention incentives, see *Section 2.3.2.6 - Other Equipment and Supplies.*

Refer participants who specifically ask for information, or a referral to their primary care provider. Remind DM Comparison participants that they will receive an annual WHI newsletter.

6.3.2 Participants Assigned to the DM Dietary Change Group (Required)

Participants randomized to the DM Dietary Change arm meet with a Nutritionist (or other designated non-blinded staff) to be assigned to a DM Intervention group. For more information about DM Intervention group formation, scheduling considerations and handling women waiting for group assignment, refer to *Section 6.8 - DM Intervention Group (Required).*

6.4 DM Intervention Goals and Design (Required)

6.4.1 Goals of DM Intervention (Required)

The goals of the DM Intervention are to:

- Reduce dietary fat to 20% of energy intake.
- Decrease intake of saturated fat to less than 7% of total energy intake.
- Increase intake of fruits and vegetables to five or more servings per day.
- Increase intake of grains and grain products to six or more servings per day.

6.4.2 Conceptual Design (Required)

The conceptual design of the WHI DM Intervention includes nutritional and behavioral themes. The three major content areas within these themes include: eating patterns, dietary change skills, and behavioral skills.

6.4.2.1 Nutritional Themes (Required)

The WHI DM Intervention is based on two nutritional themes: 1) eating patterns and 2) dietary change skills.

Eating Patterns

The specific eating patterns targeted in the DM Intervention are: 1) a reduction in fat from meat, dairy products, fats and oils, baked goods, and snacks, and 2) an increase in the use of fruits, vegetables (including beans and legumes), grains, and grain products.

These changes focus on reduction in total fat rather than type of fat which simplifies the message, increases the participant's potential success, and streamlines self-monitoring requirements. The original Women's Health Trial (WHT) found that participants automatically lowered their average intakes of saturated fat to 7% when total fat was decreased to 20% or less of baseline calories.

Dietary Change Skills

The specific information and skills required for dietary change and targeted in the DM Intervention include: 1) food selection and analysis, 2) food purchasing, 3) food preparation, 4) social dining, and 5) identification of high-risk eating situations.

6.4.2.2 Behavior Themes (Required)

The WHI DM Intervention is based on several psychosocial and behavioral themes, which are grouped into six categories: 1) reinforcements and motivators, 2) self-management, 3) skills training, 4) social support, 5) relapse prevention, and 6) self-reliance and self-efficacy.

Reinforcements and Motivators

The process of successful long-term behavior change begins with a guided self-analysis of the woman's initial motivations for participating. During the first few DM Intervention sessions, nutritionists encourage each woman to understand these motivations as a way of strengthening her resolve to change her diet. The most common motivators identified by the women in the original WHT were: 1) helping in a scientific research project; 2) personal health; 3) having a close relative or friend with breast cancer; 4) fear of cancer; and 5) learning more about nutrition.

The DM Intervention emphasizes additional motivators later in the behavior change process. These motivators include: 1) improved self-confidence and self-efficacy; 2) a sense of empowerment and self-control; 3) greater or improved social support; and 4) healthier living. The DM Intervention counters barriers to change at a very early stage. These barriers often include time and financial costs, increased awkwardness in social and eating situations, guilt about non-adherence, and decreased enjoyment when eating recommended

foods. The costs of the DM Intervention are discussed with participants throughout the sessions, and methods of minimizing cost barriers are identified continually.

Self-Management

Proven behavioral modification and self-control techniques are used throughout the DM Intervention sessions. Participants learn these techniques through a series of steps:

1. Self-monitoring of targeted behaviors.
2. Defining specific behaviors to be changed.
3. Setting quantifiable intervention goals.
4. Breaking complex behaviors down into smaller steps.
5. Specifying an action plan.
6. Obtaining evaluation and feedback on behavior changes from support network.

   Reinforcing progress and encouraging self-praise.

Skills Training

Most people need new skills to complete the process of behavior change. The original WHT identified several skills needed to modify dietary fat. Each of these skills is linked with an appropriate nutritional topic in the DM Intervention. These skills are taught and reinforced throughout the first year and include:

1. Problem-solving and analytic skills, to allow participants to handle new situations with knowledge and confidence.
2. Assertiveness and communication skills, to allow participants to actively seek out necessary foods, ingredients, and workable situations.
3. Stress-management skills, to help participants use non-eating strategies to cope with stressful situations and feelings of stress and fatigue.

   Cognitive skills, such as cognitive restructuring and imagery, to assist participants in identifying potentially dangerous self-talk and then replacing it with more healthful thoughts and feelings.

Social Support

Social support is critical for maintaining behavior change. The DM Intervention provides social support in three ways:

1. The Group Nutritionist serves as a main source of support and encouragement. Group Nutritionists are trained in listening and empathy skills. Participants learn that they can discuss any nutritional aspect of the study with their Group Nutritionist.
2. The group itself serves as a supportive environment. The tone of the group, set initially by the Group Nutritionist and maintained by the participants, has to be open, honest, sharing, and understanding. In the DM Intervention, problem-solving is a group effort and participants are encouraged to bring their most difficult situations to the group. This sharing is affirming to the participant and helps to solve the problem.
3. Family and other significant people in a participant's life provide a third source of support. Long-term dietary change is more easily maintained when it "fits" with normative family behavior. Changing a woman's eating habits often results in modifications of the family's eating habits as well. Thus, women are asked to involve their "significant others" in the change process. Problems regarding the "others'" acceptance of the low-fat eating plan are addressed as part of the DM Intervention. Most solutions will require a combination of these three sources of social support: 1) the participant asking for help, 2) receiving support from "significant others," and 3) learning to cook low-fat meals that are acceptable to "significant others."

Relapse Prevention

Maintaining behavior change requires a series of steps, known as relapse prevention strategies, to avoid the high relapse rates associated with appetite behaviors. Relapse prevention techniques are introduced during the first six months of DM Intervention. Participants identify high-risk situations such as social gatherings, emotions and changes in routines. They develop coping strategies to help them handle these high-risk situations and learn how their thoughts influence the actions they take. The women learn to think about a "high-fat" dietary behavior as a momentary lapse. They are taught to substitute "low-fat" dietary behaviors to prevent a relapse back to their original high-fat consumption pattern. Slipping back gradually to old high-fat patterns is defined specifically as low-fat dietary change relapse. Techniques for managing momentary lapses and relapses have been tested in other situations and are applied in the DM Intervention near the end of the first year. Relapse prevention is a major focus in year 2 and beyond.

Self-Reliance and Self-Efficacy

In a long-term intervention such as WHI, participants must be able to rely on their own choices and behaviors instead of a strict adherence to a prescribed dietary plan. Self-efficacy is the participant's belief that she can actually change and maintain dietary behaviors leading to a low-fat eating plan. The DM Intervention provides deliberate opportunities for participants to increase self-reliance and self-efficacy. For example, women are taught skills necessary for feeling more competent and assured in uncomfortable situations. They also learn ways to improve social support as a means of promoting confidence with new ways of eating. Group Nutritionists encourage participants to discover their own "inner power" by regularly reinforcing personal accomplishments, no matter how small. This process of empowerment and emphasis on self-control is necessary to enable women to maintain dietary changes over the long term.

6.4.3 Incorporation of Conceptual Design into DM Intervention (Required)

6.4.3.1 Daily Fat Gram Goal (Required)

Each DM Intervention participant receives a daily fat gram goal based on an algorithm that takes height into account. She makes her own food choices within the fat gram goal. There is no dietary prescription provided. The low-fat message is simplified by focusing on reductions in total fat intake. For example, one participant might choose non-fat milk while another one chooses low-fat milk and both participants are able to meet their own fat gram goal.

The CCs should not provide DM Intervention participants with the baseline grams of fat reported on the WHI *FFQ*. This instrument was intended to measure the percentage of kcalories consumed as fat, not the absolute grams of fat.

A participant who wants to determine her baseline fat intake before she starts changing her eating behaviors, may use the Food Diary assigned at Session 1 to record her usual/baseline intake instead of post-Session 1 intake. This option should be reserved only for those participants who inquire about baseline fat grams. It should not be promoted by the Group Nutritionist as the desired self-monitoring activity. At Session 2 the participant learns how to count fat grams using the Fat Counter. She can calculate her baseline fat grams from her first Food Diary at this time, however, this delays fat intake reduction by one week. Previous WHT experience indicates that participants who reduce their fat intakes early have better overall performance (attendance and fat scores).

6.4.3.2 Integration of Nutritional and Behavioral Concepts (Required)

Appropriate nutritional and behavioral concepts are integrated into each of the DM Intervention sessions and carefully ordered to produce the maximum effect. The nutritional topics in Sessions 1-8 cover the eating pattern changes that have the greatest impact on the major sources of fat in the U.S. diet (fats and oils, dairy foods, red meats, snacks and baked goods). In addition, Sessions 4-6 cover the critical dietary change skills needed for major fat changes (label reading, shopping, recipe modification, dining out). The earlier sessions introduce the concept of increasing fruits and vegetables. In later sessions (Sessions 11-14) the nutritional

topics are more specialized and include topics such as handling vacations or holidays and increasing grain and fish consumption. Nutritional topics that deal with maintenance are included later in Sessions 15-17 (i.e., changes in routine eating patterns, gradual drift in eating patterns, etc.).

Nutritional and behavioral strategies are integrated into each session for several reasons. The DM Intervention materials focus on dietary behaviors, not nutrients, as a means of decreasing fat intake and increasing fruit, vegetable and grain intake. Participants and Group Nutritionists in the original WHT were uncomfortable in group sessions where only behavioral topics were presented, so complementary nutritional and behavioral topics were included in each subsequent session in Women's Health Trial: Feasibility Study in Minority Populations (WHT:FSMP). Implementing the WHI DM Intervention eating plan means that each Group Nutritionist and participant must view dietary changes as a series of activities that will ultimately become part of everyday life. Integrating nutritional and behavioral strategies in each session also helps participants integrate them in daily life. The focus on nutritional topics is highest in the early sessions during the time of intensive dietary change. The emphasis on behavioral strategies increases during later sessions to maintain the early dietary changes.

6.4.3.3 Sequencing of Behavioral Concepts (Required)

The behavioral session topics are grouped around strategies that facilitate behavior change. The first two behavioral topics, covered during Sessions 1-3, are motivations for low-fat dietary change (i.e., family and personal health or contributing to science) and self-management (self-monitoring and goal setting). The identification and reinforcement of motivators are included in the first session to develop and maintain participants' interest in dietary change. Self-management steps form the core of necessary behavior skills. Social influences and support are included in the first nine sessions because of the critical relationship between social influences on eating and successful health behavior change. Problem-solving, cognitive restructuring, time management and coping with stress are introduced during Sessions 10-15 after the initial large decreases in fat consumption have occurred. These topics help the women incorporate the new low fat behaviors into everyday living. Finally, relapse prevention and motivation are included in the last sessions (Sessions 16-18) of the first year to assist with long-term maintenance.

An overview of the first year of DM Intervention is provided in *Table 6.3 – Summary of DM Intervention Session* (at the back of this section).

6.5 Pre-existing Diets and DM Intervention Participants (Required)

Women with pre-existing therapeutic diets may be randomized to the Dietary Change arm of the WHI. The WHI DM Intervention is modeled after the original Vanguard WHT (average 20% fat/day) and is compatible with many therapeutic meal plans. For guidelines and suggestions to help Group Nutritionists incorporate pre-existing diets into the WHI DM Intervention, refer to *Vol. 4 - Dietary Modification Intervention Group Nutritionist Manual, Section 1.1 - Guidelines for WHI DM Group Nutritionists.*

6.5.1 Participants with Diabetes (Required)

The CCs should take the steps listed below to adequately accommodate participants who have Type II diabetes in DM Intervention groups. (*Note:* Women with Type I, or insulin-requiring diabetes are not eligible for DM. Women using insulin for Type II diabetes are eligible.)

Before randomization:

- Dietary Assessment staff evaluates whether the participant can adjust to the dietary changes recommended in the DM Intervention.

After randomization, if randomized to Dietary Change arm:

- Group Nutritionist (or other designated staff) reminds participant that changing her eating habits may also change her blood glucose levels.
- Group Nutritionist (or other designated staff) refers participant to her diabetes health care team for potential adjustments to medications.
- Group Nutritionist determines the presence of participants who have diabetes prior to or at the first group session.

Refer to *Vol. 4 - Dietary Modification Intervention Group Nutritionist Manual* for more information on working with participants who have diabetes.

6.6 Nutrition Policy Issues (Required)

For information about nutrition policy issues such as definitions of and servings for fruits, vegetables and grains, general use of supplements and food handling guidelines, refer to *Vol. 4 - Dietary Modification Intervention Group Nutritionist Manual, Section 1.1 - Guidelines for WHI DM Group Nutritionists.*

6.6.1 Calcium Supplements (Required)

Group Nutritionists should not recommend calcium supplements for any WHI participants. This interferes with one of the study hypotheses in the Calcium/Vitamin D (CaD) component of the CT. DM Intervention participants may be counseled on selecting foods that are good sources of calcium. However, to recommend beyond this could be construed as treatment and be considered a co-intervention as mentioned above.

6.6.2 Donated Food Samples (Required)

Group Nutritionists can accept donated food samples provided that it is made clear to the donor (preferably in writing) that acceptance of the donation does not imply National Institutes of Health (NIH) or WHI endorsement of the product or company. It is equally important that the women receiving the food samples be made aware of this policy of non-endorsement (verbally or in writing). Specific policies and procedures are being developed.

6.7 Facility, Equipment and Supply Requirements for DM Intervention (Required)

The furniture, equipment and supplies required or recommended for DM Intervention group sessions are listed in *Section 2.3.1.2 - Supplies Provided by the CCC* and *Section 2.3.2.2 - DM Intervention.*

6.7.1 Facilities (Required)

The room(s) used for the DM Intervention group sessions are required to be large enough for groups of at least 15 participants. These rooms may occasionally be used for potlucks, cooking demonstrations and larger social functions where family members and friends are encouraged to attend.

Clinical Centers may be required to obtain group session room space outside the main clinic area as more DM Intervention groups form. Frequently churches, community centers and local libraries have rooms that they are willing to lease. When looking for outside facilities, consider the following requirements: availability of space long-term, size of room, location (easy to find, close to bus line), cooking facilities, water availability and parking.

6.8 DM Intervention Groups (Required)

6.8.1 Description of DM Intervention Groups (Required)

DM Intervention groups are permanent groups. The Clinical Coordinating Center (CCC) requires the group consist of 8-15 members and to be led by a designated Group Nutritionist.

6.8.2 Forming DM Intervention Groups (Required)

After randomization to DM Intervention, the participant meets with a Nutritionist or other non-blinded CC staff to be assigned to a DM Intervention group. The Nutritionist makes a list of potential group meeting times defined by day of week, time and location. The Lead Nutritionist (or other designated staff) uses this list to assign DM Intervention women to an available group. The Appointment Coordinator (or other designated staff) asks randomized DM Intervention participants to sign-up for a DM Intervention group. The Lead Nutritionist should be notified when 8-15 women are assigned to a group.

Participants who cannot attend any of the available groups are placed on a waiting list. The Appointment Coordinator (or other designated non-blinded staff) asks the DM Intervention participant to provide the following information for tracking participants waiting for a group assignment: name, phone number, and preferred meeting times. The CCC requires the Lead Nutritionist to use a DM Intervention group tracking sheet such as the *Table 6.4 – Sample DM Intervention Group Tracking Sheet* (at the back of this *Section 6*) or a similar CC-designed sheet when she/he schedules a new DM Intervention group (see *Section* 6.8.2.3 – *Handling DM Intervention Participants Waiting for a Group.*).

6.8.2.1 Scheduling Considerations

The Lead Nutritionist considers the following areas when forming and scheduling DM Intervention groups:

- Group size and number: The ideal group size is 12 participants but groups may contain from 8-15 women. The size of each group ultimately determines the total number of DM Intervention groups required at the CC.
- Participant requirements: Schedule groups when participants can attend (i.e., evenings and weekends, if needed) and prioritize to accommodate women who have been on the group assignment waiting list for more than eight weeks.
- DM Intervention staff availability: Consider the number, days, and times of groups taught by each Group Nutritionist. Avoid scheduling morning and evening groups for one Group Nutritionist on the same day. Also avoid scheduling groups back to back for the same Group Nutritionist. Part-time Group Nutritionist staff can lessen scheduling difficulties.
- Classroom availability: Consider using a public place in the local community such as libraries, churches, etc., if group meeting space is limited at CC.
- Maximum efficiency: Consider beginning two or three groups at the same time. This allows easy access to make-up groups when participants miss a group session. It also helps save time and labor by combining shopping and food preparation activities for several groups.
- Monthly sessions: When scheduling monthly sessions, avoid clumping by staggering groups throughout the month. Plan ahead for holidays (most are on Mondays) and prime summer vacation times.
- Lack of interruption: Whenever possible, schedule DM Intervention group sessions to allow six weekly meetings without interruption. Occasionally, the Group Nutritionist may need to skip a week in scheduling a group sessions to avoid meeting on a holiday or to accommodate central training requirements. Whenever possible, reschedule the group session within a week of its usual meeting date.
- Holidays: Try to avoid starting a DM Intervention group in December. The December holidays (Christmas, Hanukkah, etc.) are a difficult time for women to attend groups meetings and to begin

changing their eating habits. If a new DM Intervention group is formed during December, skip no more than one week of groups sessions or consider delaying the starting date of the DM Intervention group rather than skipping two weeks of groups sessions during the first six weeks. Be aware of other specific holiday periods in your area and try to schedule around them whenever possible.

6.8.2.2 Assignment of Group Nutritionist to DM Intervention Group (Required)

The Lead Nutritionist assigns a Group Nutritionist to facilitate the group, using some of the considerations listed above. The designated Group Nutritionist calls the participants assigned to her group and arranges a date for the first group meeting. After the Group Nutritionist verifies the new groups start date and list of participants, she gives her list to data entry (or other designated staff) to generate a *Form 63 - Session Data Sheet* for the first group session. Refer to *Vol. 5 - Data System, Section 8 - DM Intervention Group - Data System* for more details about DM Intervention group data entry.

Note: The Lead Nutritionist is required to lead the first DM Intervention group formed at the CC. She/he must facilitate all sessions for training and quality assurance reasons (see *Section 19 - Quality Assurance*).

6.8.2.3 Handling DM Intervention Participants Waiting for a Group (Required)

Clinical Centers need to begin DM Intervention groups whenever they have an adequate number (8-15) of DM Intervention participants available. The goal is to have DM Intervention women in groups by three months post-randomization (12 weeks). After a new DM Intervention group begins, the Lead Nutritionist selects a time slot for the next group to start. She/he selects times that accommodate participants who have been on the group assignment waiting list for more than eight weeks, as well as other considerations listed above (see *Section 6.8.2.1 – Scheduling Considerations*).

All DM Intervention participants who have not started DM Intervention (i.e., completed Session 1 or more) are required to be contacted at least once a month by phone or mail. If DM Intervention groups are formed more frequently than once a month, a participant does not need to be called more than once a month. The Lead Nutritionist (or other designated staff) contacts the DM Intervention participants on the DM group waiting list to:

- Maintain interest in the program (this is particularly important if groups are formed less frequently than once a month).
- Determine if a participant's availability for groups has changed (record new times).
- Determine if a participant can attend a new group that is forming.

The staff member calling uses a DM Intervention group tracking sheet (see *Table 6.3 – Sample DM Intervention Group Tracking Sheet* or similar CC-designed sheet) to record the dates when the participant is contacted by phone. If a CC is unable to reach the woman by telephone, after at least three attempts at different times of the day, she is contacted by mail. The CCC strongly recommends that the CC's group tracking sheet contain the following information: name, preferred group times, phone number, date reached (phone or mail), and comments column to record group assignment and changes in group scheduling needs. Depending on the CC's needs, the group tracking sheet might also contain some of the following information: date of randomization, date of goal to be in a group (12 weeks post-randomization), and best times to call the woman. The CCC requires the CC to record the reason a DM Intervention participant is not assigned to a group. The Lead Nutritionist uses this DM Intervention group tracking system when she/he schedules a new DM Intervention group. Refer to *Vol. 5 - Data Systems, Section 8 - DM Intervention Group Data System* for information about reports that track DM Intervention startup and unassigned DM members.

In the initial three to six months of the Dietary Trial, slow recruitment rates may interfere with the establishing groups in a timely manner. During this time period, the DM Intervention participants interest may be maintained by using the procedures recommended in *Section 6.8.3 – Maintaining Interest in Women Waiting for DM Intervention*. It is very important to get women into groups as soon as possible after randomization. The Group Nutritionist has the option to proceed with a DM Intervention group assignment and provide a participant with catch-up sessions on an individual basis, rather than allow a woman to wait 12 or more weeks

for assignment to a DM Intervention group. The Lead or Group Nutritionist uses her own best judgment to make this decision. However the following criteria must be met before a participant who receives individual catch-up sessions is placed in an ongoing DM Intervention group:

- The participant will be unavailable to start another DM Intervention group in a reasonable amount of time (i.e., three months).
- There is an ongoing DM Intervention group that has only covered Sessions 1-3 (ideally not more than Session 2). The Group Nutritionist schedules an individual visit with the participant, prior to her attendance in the DM group and completes *Form 64 - Individual Data Sheet* for each session covered. No more than three sessions can be made up in an individual visit.
- The group members in the ongoing group have no reservations about having a new group member.
- The group enrollment in the ongoing group will not exceed 15 group members with the addition of the new participant.

If a woman has been randomized in DM Intervention but is unable to join an Intervention group, refer to *Section 6.10.6.3.1 – Awaiting Start-Up of DM Intervention* for procedures.

6.8.2.4 Final Group Formation at the End of Recruitment

The principle to use when planning final Dietary Change group formation is to arrange for as many participants as possible to receive as much of the DM Intervention as possible. Participants should be assigned to active groups, rather than creating a separate "straggler" group(s) which will never actually meet. This approach will best provide the mechanism to deliver the intervention to all active Dietary Change participants (by intervention as designed or Interrupted DM Intervention Participation). Nutritionists will also find it a more streamlined procedure.

Use the following hierarchy when planning final Dietary Change groups:

- First option: Form groups per usual procedure (to preserve the concept of group social support for new groups and minimize changes to existing groups). Screen women for availability to attend sessions of the final groups.
- Second option: Assign women to recently formed groups and use makeup sessions to catch these women up to the group's session schedule. This option will work for women willing and able to attend sessions, though unable/unwilling to attend the last groups forming. Nutritionists should attempt to assign women to groups that are as near the beginning of intervention as possible (e.g., within the first six sessions). The final assignment decision should be based on balancing a participant's ability to catch up, existing group dynamics, and staffing considerations.
- Third option: For those participants who are unable/unwilling to attend group sessions with either existing or the last groups forming, use Interrupted DM Intervention Participation procedures to deliver as much intervention as possible in as efficient a manner as possible. Refer to *Section 6.10.6.3 (including all subsections) – Interrupted DM Intervention Participation Procedures.*

6.8.3 Maintaining Interest in Women Waiting for DM Intervention (Required)

If a randomized DM Intervention woman has been waiting <u>at least one month</u> for her first group meeting, send the participant the written post randomization material: "Your New Eating Style." The material can be given to the woman in person or sent to her in the mail. Refer to *Vol. 4 - Dietary Modification Intervention Group Nutritionist Manual, Section 4 - Post-Randomization Intervention Material* for a copy of this introductory material.

The purpose of the introductory material is to provide some guidance and motivational information for women randomized to the Dietary Change group who are waiting for their first DM Intervention group session.

The CC may use other types of activities (instead of, or in addition to, the booklet "Your New Eating Style") to maintain interest and motivation (i.e., introductory sessions including food tasting and get acquainted

activities, etc.). However, a CC that wants to use a different activity to maintain interest during the "down time" between randomization and the start of DM Intervention groups is required to submit their plans/ideas in writing to the CCC for approval at least one month prior to the planned activity.

If a DM Intervention participant cannot attend the scheduled introductory activity, the CCC requires the CC to arrange for the participant to receive another form of communication. For example, the CC could mail the woman the supplementary materials from the CC introductory group activity, or provide her with the introductory booklet: "Your New Eating Style." A nutritionist should follow this mailing with a telephone call.

6.8.4 Combining DM Intervention Groups in First Year (Required)

During the first year, DM Intervention groups should be maintained with the same group of women assigned at randomization and with the same Group Nutritionist. Groups should not be combined during the first year of DM Intervention.

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6.9 DM Intervention (Required)

6.9.1 Group Nutritionist and Participant Manuals (Required)

Group Nutritionists trained and certified by the CCC deliver the DM Intervention. The DM Intervention uses a group teaching format and integrates nutritional and behavioral content within each session.

Vol. 4 - Dietary Modification Intervention consists of two parts, the *Group Nutritionist Manual* and the *Participant Manual*. The CCC provides each CC with five copies of *Vol. 4.* Three copies are for Group Nutritionist use (CCs with remote sites receive four copies for Group Nutritionists) and the other two copies are for general CC use.

6.9.1.1 Group Nutritionist Manual (Required)

The *Group Nutritionist Manual* includes the materials needed to facilitate the first year of DM Intervention Sessions (1-18, and Individual Session). The materials for each session include: session objectives, materials needed, suggestions for food tasting, *Participant Manual* page references and a suggested outline and procedures for the session.

In addition, the *Group Nutritionist Manual* contains information about handling pre-existing diets, nutritional policy issues, group facilitation, suggested readings and low-fat cookbooks, and a copy of the post-randomization DM Intervention material: "Your New Eating Style."

6.9.1.2 Participant Manual (Required)

Each DM Intervention participant receives a *Participant Manual* containing worksheets used during the group sessions and specific nutritional and behavioral information. The session information is written as self-help material and is designed to help women who miss class keep up with their group. The women are not required to read the materials if they come to class.

In addition, each participant receives a Fat Counter, Food Diaries, Fat Scans, recipes and supplementary handouts. The CCC provides Spanish versions of all participant materials for women who speak or read Spanish.

6.9.2 DM Intervention Schedule (Required)

During the first year, the participant attends group sessions once a week for six weeks, once every two weeks for six weeks, and once a month for nine months, for a total of 18 group sessions. Each participant also has one Individual Session with her Group Nutritionist. Beginning in the second year, there are four required maintenance sessions scheduled for each group per year.

6.9.3 Individual Session (Required)

The Group Nutritionist schedules an Individual Session with each group member between Sessions 9 and 10. The interval between these two sessions is normally one month (four weeks). However, this interval, between Session 9 and 10, may be extended (per Group Nutritionist discretion) to six weeks if needed to complete all Individual Sessions between Session 9 and 10.

The Individual Session lasts approximately 45 minutes and follows the outline and procedures detailed in "Individual Session," *Vol. 4 - Dietary Modification Intervention Group Nutritionist Manual*. The Group Nutritionist completes *Form 64 - Individual Data Sheet* for each Individual Session. *Note:* The Individual Session is different from other individual visits that would be scheduled for such activities as make-up or additional assistance (see *Section 6.10.5 – Make-Up Activities for Women Who Miss Sessions* and *Section 6.11 – Participant Progress*).

The Group Nutritionist will not have nutrient data available to look at nutritional adequacy issues. However, self-monitoring tools (Fat Scans and Food Diaries) can be used to assess the overall nutritional balance of a participant's food choices and identify areas that need to be changed. The Group Nutritionist should use the Individual Session as an opportunity to:

- Give each participant individual support and feedback.
- Discuss dietary changes.
- Evaluate variety and balance of current eating patterns.
- Identify potential compliance problems and plan for long-term maintenance.

Scores: Collecting and Recording

The total number of Fat Scans assigned between Sessions 9 and 10 is determined by the length of the interval between the sessions. The Group Nutritionist assigns the number of Fat Scans necessary to maintain a biweekly self-monitoring schedule. The number of Fat Scans assigned at Session 9 and the Individual Session depends on the placement of the Individual Session between Sessions 9 and 10. The Group Nutritionist assigns the appropriate number of Fat Scans at Session 9 and the Individual Session using *Table 6.1-b – Number of Fat Scans to Assign Dependent on Placement of Individual Session (6-Week Interval)*.

The Group Nutritionist collects the scores from Fat Scans assigned at Session 9 at the Individual Session and records them on *Form 64 - Individual Data Sheet*. Scores from Fat Scans assigned at the Individual Session are collected at Session 10 and recorded on *Form 63 - Session Data Sheet* (or *Form 64*, if doing make-up). If a participant does not complete the assigned score(s), the Group Nutritionist collects the score(s) at a later date using the procedures outlined in *Section 6.9.5.3 – Self-Monitoring Procedures*.

Home Activity: Collecting and Recording

The Group Nutritionist collects the Home Activity assigned at Session 9 at the Individual Session and records its completion of *Form 64 - Individual Data Sheet*. Home Activity assigned at the Individual Session is collected at Session 10 and recorded on *Form 63 - Session Data Sheet* (or *Form 64*, if doing make-up).

Table 6.1a
Number of Fat Scans to Assign Dependent on Placement of Individual Session (4-Week Interval)

4-Week Interval Between Session 9 and Session 10				
Number of weeks between **Session 9** and **Individual Session**	Number of Fat Scans Assigned at **Session 9**	Number of weeks between **Individual Session** and **Session 10**	Number of Fat Scans Assigned at **Individual Session**	**Total Number** of Fat Scans
0	**0**	4	**2**	**2**
1	**1**	3	**1**	**2**
2	**1**	2	**1**	**2**
3	**1**	1	**1**	**2**
4	**2**	0	**0**	**2**

Table 6.1b

Number of Fat Scans to Assign Dependent on Placement of Individual Session (6-Week Interval)

6-Week Interval Between Session 9 and Session 10				
Number of weeks between **Session 9** and **Individual Session**	Number of Fat Scans Assigned at **Session 9**	Number of weeks between **Individual Session** and **Session 10**	Number of Fat Scans Assigned at **Individual Session**	**Total Number** of Fat Scans
0	**0**	6	**3***	**3**
1	**1**	5	**2**	**3**
2	**1**	4	**2**	**3**
3	**1**	3	**1**	**3**
4	**2**	2	**1**	**3**
5	**2**	1	**1**	**3**
6	**3***	0	**0**	**3**

Note(*): If a participant turns in more than two fat scores (or fruit/vegetable or grain scores) at one session, the Group Nutritionist must average the scores before they are key entered into the WHILMA database. For example, if a participant turns in three fat scores (e.g., 30 g, 34 g, 27 g) at one session, the Group Nutritionist would record the average of the scores (e.g., 30) on *Form 63* (or *Form 64* if doing make-up) for the session.

6.9.4 Group Sessions (Required)

6.9.4.1 Content and Length (Required)

DM Intervention sessions are designed to take 1-1/2 to 2 hours. The schedule, session objectives and nutritional and behavioral topics for the first year of DM Intervention sessions are shown in *Table 6.2 – Summary of DM Intervention Sessions*.

6.9.4.2 Delivery of Group Sessions (Required)

The DM Intervention uses a variety of educational techniques to increase the participant's level of interest and retention of information. It is recommended that the use of lecture be limited and that the majority of class time be spent on interactive activities. Session activities give participants an opportunity to practice skills during group sessions. This lets participants anticipate problems and develop solutions before they leave the supportive group environment.

To maintain the sequence of key behavioral topics and ensure that all DM Intervention participants receive similar information, the Group Nutritionist is required to present the sessions in the same order as written (i.e., Session 5 must be presented before Session 6). DM Intervention sessions are designed to build on each other (see *Section 6.4.3 – Incorporation of Conceptual Design into DM Intervention*).

Group Nutritionists can modify the foods served or examples used in DM Intervention sessions to accommodate group interests and food preferences. For example, if the session on cognition (Session 11 - Self-Talk) is covered during the winter months, the examples used for food tasting and group discussion could focus on holiday situations and foods instead of lunches as written.

6.9.4.3 Format of Group Session (Required)

Each DM Intervention session consists of five parts: review of previous home activity, new material, summary, assignment of new home activity and food tasting. The following briefly summarizes the purpose of each of these sections and the Group Nutritionist's role in the process.

Review of Previous Home Activity

The Group Nutritionist is required to begin each DM Intervention session with a review of the previous home activity assignment. This review allows the participant to evaluate the goals she set and discuss behavioral and dietary successes and challenges that occurred during the previous period. In addition, it gives the participant an opportunity to provide support and guidance to other group members. The Group Nutritionist's primary role is to facilitate group discussion. She/he should use the group discussion to emphasize positive behaviors and provide reinforcement and direction for selection of appropriate strategies.

New Material

The major part of the group session presents new information or ideas to the group and lets them practice the skills or concepts within the supportive group environment. This section also provides the structure for each individual to gather information and select a specific topic-related goal to work on before the next session. The Group Nutritionist's primary role is to present the new information, guide group discussion using facilitation skills, and help the group members help each other. The Group Nutritionist should encourage equal participation among group members, encourage positive support and feedback, keep the group on topic, summarize the group at appropriate points and ask for feedback. The Group Nutritionist should facilitate horizontal interaction (participant to participant) versus vertical interaction (participant to Group Nutritionist).

Summary

Near the end of each DM Intervention session there is a brief summary required. The purpose of this section is to provide an opportunity for formative evaluation by assessing the participant's understanding of the ideas and skills presented during the session. It allows the Group Nutritionist to evaluate the group's ability to accomplish the objectives outlined for the session and provides an opportunity to reinforce learning. The Group Nutritionist's primary role is to briefly summarize the key points and then ask open-ended questions that allow the participants to process the information they have received during the session. The Group Nutritionist should also use the participants' responses during the discussion to clarify any misunderstood concepts.

Home Activity Assignment

At the end of each session participants receive an assignment to complete at home. The purpose of this assignment is to allow the participants to identify specific goals and action plans they will use between DM Intervention sessions. The home activity assignment provides an opportunity for the participants to use the nutritional and behavioral information they received during class and to measure their progress. The Group Nutritionist's role is to ensure that all participants understand the importance of this assignment and outline the areas where the participants should be setting their goals. For details on handling Home Activity Worksheets see *Section 6.10.4.3 – Home Activity Worksheets (Required)*.

Food Tasting

Each group session includes food tasting. The provision of food tasting allows the participants to sample new foods, modified traditional favorites and foods prepared with new cooking techniques. The Group Nutritionist's role is to see that the food is prepared using safe food handling techniques and presented in a way to encourage participant use. The Lead Nutritionist uses nutrition support staff (if available) to assist Group Nutritionists with the preparation of foods and classroom materials. The Lead Nutritionist coordinates shopping, preparation, storage and service of food items as dictated by availability of staff, space and equipment. The Lead Nutritionist modifies food-tasting suggestions, if necessary, to accommodate cooking resources and/or regional food preferences; however, foods sampled in a session should reflect the session's message. The Lead Nutritionist ensures that intervention staff always use safe food handling procedures. For more information on food handling guidelines, see *Vol. 4 - Dietary Modification Intervention Group Nutritionist Manual, Section 1.3 - Food Handling Guidelines.*

6.9.5 Self-Monitoring (Required)

Self-monitoring is an essential part of the DM Intervention. The self-monitoring tools allow the participant to monitor her intake of fat, fruit/vegetable and grain servings, and to calculate the following scores:

- Fat score (average grams of fat consumed per day)
- Fruit/vegetable score (average fruit/vegetable servings consumed per day)
- Grain score (average grain servings consumed per day)

6.9.5.1 Aims of Self-Monitoring

The aims of self-monitoring are to:

- Increase the participant's awareness of her food intake.
- Teach the participant how to make wise food choices while decreasing fat and increasing fruits, vegetables and grains.
- Assist the participant in monitoring her progress during the DM Intervention.
- Provide the Group Nutritionist with information about a participant's dietary intake.
- Provide methods to monitor dietary change data over time.

6.9.5.2 Self Monitoring Tools (Required)

The DM Intervention uses two different self-monitoring tools: the Fat Counter with the Food Diary and the Fat Scan. Participants use the Fat Counter with the Food Diary during the first two months of group sessions (Sessions 2-6) and then replace them with the shorter Fat Scan at Session 7.

Fat Counter and Food Diary

The WHI Fat Counter was expanded from the Fat Counter used in the WHT:FSMP. It contains approximately 1,000 foods listed in two sections, one which is alphabetical and one which is by food group. The Fat Counter gives fat grams per serving for each food item and also lists servings of fruit/vegetables and grains in color-coded columns. The fat gram values in the Fat Counter are from the Minnesota Nutrient Data System (NDS) which the CCC uses to analyze all WHI dietary data. NDS Version 2.6. was used to calculate the fat gram values in the WHI Fat Counter. The DM Intervention participants begin using the Fat Counter at Session 2. A participant uses the Food Diary to record everything she eats or drinks for a minimum of three days (including one weekend day) each week. She uses the Fat Counter to look up the grams of fat in each food. She adds the grams of fat for each day and divides by the total number of days recorded to calculate her fat score.

The Food Diary contains an optional "fat-o-meter" (see Food Diary) that requires minimal math skills. A participant may use this method to track of the grams of fat she consumes and calculate a fat score. The meter is a scale with numbered dots that can be marked off as fat grams accumulate.

Fat Scan

The Fat Scan is a shorter and quicker method of monitoring fat intake that also allows monitoring of fruit/vegetable and grain consumption. The Fat Scan contains approximately 260 foods listed by food group. The food groups include: 1) breads, cereals and grain products; 2) dairy products; 3) fats, oils, nuts and sauces; 4) fruits, salads and vegetables; 5) meat, poultry and fish; 6) mixed dishes, and 7) sweets and desserts. The fat grams in the Fat Scan are from the same database (i.e., Minnesota NDS) used in the Fat Counter. The Fat Scan gives fat grams per serving for each item and color codes fruit/vegetable and grain sources for easy identification. A participant does not keep a separate Food Diary when using the Fat Scan. As a participant consumes food, she circles the items in the Fat Scan. At the end of the day she adds the circled numbers (fat grams) to calculate her fat intake and counts the servings of fruits/vegetables and grains. She records her food intake for three days and calculates her scores by averaging the daily totals. Participants use the Fat Scan beginning at Session 7 and continue to use them at every session during the first year.

6.9.5.3 Self-Monitoring Procedures (Required)

The Group Nutritionist encourages all participants to use the self-monitoring tools provided (Food Diary and Fat Scan) and turn them in after completion. Ask the participant to complete at least one 3-day self-monitoring tool for each session.

Collecting and Recording Scores

At the end of each session, collect the self-monitoring tools. Record the self-monitoring scores, assigned at the previous session, on *Form 63 - Session Data Sheet*. If the participant does not bring a completed self-monitoring tool to the session, leave the "score" column blank on *Form 63* (or *Form 64*, if doing make-up). Encourage the participant to complete the self-monitoring tools. If the participant completes the self-monitoring tools after the session, go back to *Form 63* (or *Form 64*, if doing make-up) for that session and record the scores. In addition to recording the scores, record the number of days the participant recorded her food intake. See Vol. 3 Forms instructions for *Form 63 - Session Data Sheet* and *Form 64 - Individual Data Sheet*.

Reviewing Self-Monitoring Tools

Review the completed Food Diaries or Fat Scans, prior to the next session, for accuracy of calculations and maintenance of healthy low-fat eating behaviors. Return the self-monitoring tool to the participant at the next session with corrections and comments which praise progress and note problems. Provide a clear message to participants that the Group Nutritionist uses the participant's self-monitoring scores to track their progress and provide additional assistance as needed.

Note: The Group Nutritionist encourages DM Intervention participants to self-monitor on a regular basis and uses the information to track progress. The Group Nutritionist monitors individual progress using the procedures outlined in *Section 6.10 (including all subsections) – DM Intervention Participation* and *Section 6.11 (including all subsections) – Intensive Intervention Protocol (IIP)*. The Group Nutritionist monitors group progress using the procedures outlined in *Volume 7 - QA, Section 5 – Data Monitoring*. DM reports available in WHILMA help the Group Nutritionist track individual and group progress. Refer to *Vol. 5, Section 8.2 – DM Intervention Group Reports* and *Vol. 5, Appendix D – WHILMA Reports* for information about DM reports.

The CCC monitors self-monitoring data. Quality assurance performance goals for self-monitoring are outlined in *Volume 7 – QA, Section 6 – Performance Monitoring*.

Use of Whole Numbers or Fractions

Participants use whole numbers or fractions/decimals per individual preference, in the self-monitoring tools. The Group Nutritionist instructs the participants who choose to record only whole numbers to use the following rounding rule: round up to the next whole number if the fraction/decimal is greater or equal to 0.5; and round down to the previous whole number if the fraction/decimal is less than 0.5.

The Group Nutritionist records the scores on the data collection forms (*Form 63 - Session Data Sheet* and *Form 64 - Individual Data Sheet*) as follows:

- If the participant reports scores as whole numbers, the Group Nutritionist records the scores as whole numbers.
- If the participant reports scores as decimals, the Group Nutritionist records the scores as decimals. The computer automatically completes the decimal rounding.
- If the participant reports scores as fractions, the Group Nutritionist records the scores as decimals. The computer automatically completes the decimal rounding.

Handling Incorrect Fat Scores

If the Group Nutritionist discovers an error in a participant's fat, fruit/vegetable or grain score(s), she/he records the correct score on *Form 63 - Session Data Sheet* or *Form 64 - Individual Data Sheet*. Refer to *Section* and *Vol. 3 - Forms* for more details about use of *Form 63* and *Form 64*. If the Group Nutritionist

discovers an error after either of these forms have been data entered, she/he notifies the CC data entry staff that the score(s) requires correction.

6.9.5.4 Self-Monitoring Issues

During the study, there might be a percent of participants who do not self-monitor. Some typical reasons that have been given in other studies include boredom or fatigue, lack of perceived benefit from ongoing record keeping, inability to make self-monitoring part of daily routine, and math/literacy problems.

DM Intervention participants may have some difficulty maintaining self-monitoring. Group Nutritionists may need to spend extra time helping participants learn how to keep records and use the various self-monitoring tools. It is also critical that participants understand the importance of self-monitoring as it relates to achieving their goal and to the study. However by using the following activities, some form of self-monitoring can be maintained throughout the study:

- Provide a clear message about self-monitoring expectations during screening visits.
- Provide clear self-monitoring instructions early in the DM Intervention process (Session 2).
- Provide a variety of self-monitoring tools (Fat Counter and Food Diary in early sessions, Fat Scan in later sessions and alternative tools for participants who are unable or unwilling to use the Food Diaries or Fat Scans.)
- Require a minimum of three days.
- Provide a math-easy option ("fat-o-meter").

Although some self-monitoring should continue throughout the study, the amount can probably be reduced at the beginning of the year 2. Starting with year 2, the requirement for self-monitoring is reduced to a minimum of three days per month compared to the three days every two weeks in year 1. The Group Nutritionist should encourage DM Intervention participants who wish to self-monitor more frequently to do so. The Group Nutritionist may recommend a more frequent self-monitoring schedule when a participant is having trouble attaining goals.

If participants have difficulty self-monitoring, the Group Nutritionist may want to consider using some of the following suggestions to promote self-monitoring:

- Use-alternative self-monitoring tools.
- Use self-monitoring tools without looking up fat grams or calculating fat scores (i.e., keeping a Food Diary without looking up fat grams).
- Use self-monitoring tools for only one or two days instead of three or more days.
- Individualize self-monitoring requirements as the study progresses.

The possibility of making other easy-to-use self-monitoring tools available, such as a checklist system, will be considered.

6.9.5.5 Alternative Self-Monitoring Tools:

Alternative self-monitoring tools were developed to enhance adherence to dietary and self-monitoring goals and to encourage self-monitoring for women experiencing problems with the usual tools. Participants should be given ample opportunity to learn to use the usual tools prior to introducing the alternatives. Wait until maintenance sessions to introduce these tools to participants, however, if needed they may be introduced as early as session 12.

The alternative tools address issues that interfere with self-monitoring.

- A simpler and more portable format.
- A graphic format.

- A behavioral and less mathematical manner of monitoring.
- A need for "change," particularly for women who have reached years two and three in maintenance.

Score generating self-monitoring tools likely give participants a better picture of their adherence to dietary goals than do behavioral tools. Therefore, behavioral tools are ideally offered to participants unable or unwilling to use score generating tools or who express interest in using a behavioral tool in addition to a score generating tool.

Keeping Track of Goals

A participant uses the Keeping Track of Goals to record her fat, fruit/vegetable and grain intake. The participant checks a box for each fruit/vegetable and grain eaten and records fat grams for meals and snacks for up to 6 days per form. It is appropriate to use during maintenance with participants who are familiar with fat gram values, working women who need to keep diaries at home and work and for those who eat the same foods regularly.

Quick Scan

The Quick Scan is similar to the Fat Scan, except that it is only two pages. The Quick Scan lists commonly eaten foods and includes space to add foods. The Quick Scan may be tailored to suit regional preferences by adding or substituting foods on a master copy. Like the Fat Scan, the foods are listed by food groups and list Fat, Fruit/Vegetables and Grain servings. The Quick Scan has space to record three days intake and participants average the three days to calculate their scores.

Picture Tracker

The Picture Tracker was designed to provide a graphic tool for participants who are visually impaired or who find record keeping tedious and prefer a quick visual tool. It is offered to participants who are not turning in any records. Participants count servings of Fruits/Vegetables and Grains. Participants are asked to list low-fat and high-fat foods, but they do not record fat grams. Only one day's food intake is recorded per record.

Eating Pattern Changes

The Eating Pattern Changes questionnaire tracks behavior changes in eating. The behaviors tracked include key fat reduction strategies (e.g. reducing fat from snacks, desserts, meats, dairy, added fats and using assertiveness skills). In addition, participants record goals to help them achieve their dietary goals .

This tool is appropriate for women who have never monitored or who dislike the current method of monitoring or who are having trouble with math and those who may be at risk for adherence. This tool encourages participants to self-assess behaviors and to identify the goals they need to achieve. The Eating Pattern Changes questionnaire may help motivate participants to eventually return to using the Fat Scan and Food Diary, because it emphasizes the positive changes participants are making in their diet.

6.10 DM Intervention Participation (Required)

Attendance at all DM Intervention sessions is important. Attendance during the first six months (Sessions 1-12) is particularly critical because the information given to participants during these sessions is the foundation of the DM Intervention.

At the Screening Visit 3 (SV3), before randomization, a certified Lead Nutritionist, Dietary Assessment staff, or Group Nutritionist is required to use the *DM Eligibility Checklist* to assess a participant's ability to complete the activities of the DM Intervention. For more information about this review process and DM eligibility status, see *Section 6.2 – SV3 Assessment of DM Eligibility* and *Section 6.2.1 – DM Eligibility Checklist.*

6.10.1 Travel and Group Participation (Required)

During the first six months, the DM Intervention covers the basic nutritional and behavioral skills required to change eating patterns. It also provides time for the Group Nutritionist and the group members to develop rapport and group bonding.

Currently, there are no provisions for "drop-ins" to DM Intervention group sessions at other CCs. Therefore, the CCs should try to identify prior to randomization, participants who travel away from their home for extended periods of time. (Refer to *Form 2/3 - Eligibility Screen.*) The Group Nutritionist must make every attempt to encourage active participation of women randomized to DM Intervention. For more detailed information about determining levels of DM Intervention participation, see *Section 6.10.6 – Determining and Maintaining Levels of DM Intervention Participation (Required).*.

6.10.2 Family and Friends Attendance at Group Sessions

Group Nutritionists may encourage participants in the DM Intervention groups to bring family members and/or friends, dependent on the size of the meeting room and the feelings of other group members. However, Control participants in DM or any participants who are randomized to other components of WHI (OS and HRT) cannot attend DM Intervention sessions. This could confound the results of the study.

6.10.3 Methods to Encourage Participation (Required)

To encourage regular attendance, each CC emphasizes the significance of attendance during both pre- and post-randomization visits.

6.10.3.1 Pre-Randomization Methods (Required)

- Discuss and review the demands of the DM Intervention class schedule at all screening visits.
- Verify the participant's availability to attend for the first six months of DM Intervention sessions (Sessions 1-12). *Form 2/3 - Eligibility Screen* gathers information on a participant's availability. Refer to *Section 6.1.5 – Availability During Next Year* for more detailed information about DM eligibility.

6.10.3.2 Post-Randomization Methods

- Schedule DM Intervention sessions at times that are convenient for participants (i.e., avoid holidays whenever possible, locate group meetings in local neighborhood churches, libraries, etc.).
- Verify the participant's ability to attend at least the first six sessions before class assignment is made.
- Encourage the participant to take responsibility for attendance, including notification of CC staff if she is unable to attend a scheduled session.

- Involve the participant in maintaining the group's attendance by using a participant phone tree or buddy system established early in the DM Intervention (optional).
- Display graphs of group attendance at DM Intervention sessions (optional).
- Increase the participant's motivation and interest by providing feedback on the participant's self-monitoring tools.
- Phone DM Intervention participants or mail them reminder postcards (at least 1-1/2 weeks prior to scheduled session) during the monthly and maintenance sessions.

6.10.4 Monitoring Participation (Required)

The Group Nutritionist uses the following forms and tools to keep track of participant's progress and DM participation:

- *Form 63 - Session Data Sheet*
- *Form 64 - Individual Data Sheet*
- Home Activity Worksheets
- Group Nutritionist Progress Notes

6.10.4.1 Session Data Sheet (*Form 63*) (Required)

Form 63 - Session Data Sheet documents the following:

- Group session attendance.
- Completion of home activity.
- Fat, fruit/vegetable and grain scores.
- Make-up activities (date of Group Nutritionist phone call and reason for absence).

At each session, the Group Nutritionist documents attendance and other data described above using *Form 63*. She/he assures that the data entry of *Form 63* is completed before the group's next DM Intervention session. If the Group Nutritionist is unable to reach absent participants before the form is sent to Data Entry, the following data fields are left blank: date of phone call and reason for absence. *Form 63* can be updated when the data become available. See *Vol. 3 - Forms, Form 63* Instructions for details.

6.10.4.2 Individual Data Sheet (*Form 64*) (Required)

Form 64 - Individual Data Sheet documents various types of individual contact and includes data similar to that found on *Form 63 - Session Data Sheet*. The Group Nutritionist must use *Form 64* to document required individual DM Intervention contacts. Required individual DM Intervention contacts include:

- Missed session makeup.
- Individual Session (required between Sessions 9 and 10).
- Intensive Intervention Protocol (IIP) contacts.

The Group Nutritionist may use *Form 64* at CC discretion to document optional individual DM Intervention contacts. Optional DM Intervention contacts include any non-required individual DM Intervention contacts. Optional contacts are marked "Other" on *Form 64*.

The Group Nutritionist (or other designated CC staff) completes data entry of *Form 64 - Individual Data Sheet* within one week of the individual contact, whenever possible. See *Vol. 3 - Forms, Form 64* Instructions for details on the use of *Form 64 - Individual Data Sheet*

6.10.4.3 Home Activity Worksheets (Required)

The Group Nutritionist monitors completion of Home Activity Worksheets and records this information on the *Form 63 - Session Data Sheet* or *Form 64 - Individual Data Sheet* as described above. The Group Nutritionist may monitor completion of the Home Activity Worksheet by collecting and reviewing the worksheets after each session or she/he may choose to evaluate completion of the Home Activity Worksheets based on participant responses during the Review of Home Activity discussion that occurs at the beginning of each session. If the Group Nutritionist chooses the latter option, she/he will not have the opportunity to make written comments on the worksheets, which may be valuable for some participants. In addition, the Group Nutritionist should allow adequate time in the group discussion to evaluate completion of Home Activity Worksheets by all participants if the worksheets are not collected.

6.10.4.4 Group Nutritionist Progress Notes (Required)

The Group Nutritionist keeps progress notes on each individual in every DM Intervention group she/he facilitates. These notes help her/him to personalize the DM Intervention sessions and provide background information for the Individual Session. Progress notes may include information about food preferences or intolerances, family support, special situations such as illnesses or work schedules and other personal commitments. The CCC does not require the use of a special form to record progress notes. The notes should be dated and kept in a notebook or file for each DM Intervention group. Depending on the requirements of each CC's institution, the Group Nutritionist progress notes may need to be kept in a locked cabinet or as part of the medical record.

6.10.5 Make-Up Activities for Women Who Miss Sessions (Required)

This section describes the procedures a Group Nutritionist is required to use when a participant misses a DM Intervention group session(s).

6.10.5.1 Procedures for Communicating with Women Who Miss Sessions (Required)

Group Nutritionists use standardized procedures for contacting non-attendees between sessions to maintain participation, identify problems and arrange for make-up of missed sessions. Immediate contact after a missed session makes the woman aware of the importance of attendance and strengthens her commitment to the study.

The make-up procedures described in the section are minimal requirements. Clinical Centers are encouraged to develop additional methods that will promote group attendance. For example, the CCs could decide to schedule an individual meeting for a participant who has missed one or two sessions during the biweekly or monthly group sessions. Group Nutritionists must complete *Form 64 - Individual Data Sheet* whenever make-up activities involve individual participation, whether it is in person, by phone or by mail.

Participant Misses Session Without Notification

Whenever a participant misses a session without notifying the Group Nutritionist in advance, the Group Nutritionist communicates with the participant using the following procedures:

- Calls the woman by telephone within one week. A minimum of three attempts at different times of the day are made to reach the participant.
- Sends a follow-up letter if the participant cannot be reached by phone and asks her to call the clinic as soon as possible.
- Makes a follow-up call if the participant fails to respond to the letter within one week.

When the Group Nutritionist reaches the participant for make-up, she/he uses the following procedures:

- Records the participant's reason for the absence and the date the participant was reached to schedule a make-up activity on *Form 63 - Session Data Sheet.*
- Schedules a participant make-up activity (see *Section 6.10.5.2 - Description of Make-Up Plans for Women Who Miss Sessions*).

- Mails the missed session material to the participant if she doesn't already have the materials and cannot attend another group's session. Mail make-up activities cannot be easily used during the first six weeks because of the lack of sufficient time between DM Intervention sessions.

Participant Misses Session With Notification

Whenever a participant misses a session but notifies the Group Nutritionist in advance, the Group Nutritionist can either give her the missed session materials early or mail them to her, if she doesn't already have them. The Group Nutritionist records the participant's reason for absence and the date the participant was reached to schedule a make-up activity on *Form 63 - Session Data Sheet* as follows:

- If the Group Nutritionist arranges make-up of the missed session when the participant notifies her of the absence, the Group Nutritionist records the date the woman notified her as the call date on *Form 63 - Session Data Sheet*.
- If the Group Nutritionist does not arrange make-up of the missed session when the participant notifies her of the absence, the Group Nutritionist records the date she reaches the participant to schedule the make-up as the call date on *Form 63 - Session Data Sheet*.

6.10.5.2 Description of Make-Up Plans for Women Who Miss Sessions (Required)

Whenever a participant is absent she is required to make up the session. The make-up plan depends on the number of DM Intervention sessions the woman has missed, the Group Nutritionist's workload and the participant's availability. It also depends on whether the session(s) missed is one or more of the first six DM Intervention sessions.

Participant Misses 1-2 Sessions At Any Time

If a woman misses one or two sessions at any time during the study, the Group Nutritionist uses <u>one</u> of the methods described below:

- Allows the woman to attend another DM Intervention group that is covering the missed session(s) material.
- Mails the woman the missed session(s) material (if she doesn't already have it) and asks her to complete the worksheets, furnish self-monitoring data and attend an individual meeting with the Group Nutritionist. The meeting may occur at any time before or after the next group session. The Group Nutritionist uses the meeting to review the session material, respond to participant questions, discuss ongoing challenges and collect self-monitoring data.
- If the woman cannot come in for an individual meeting before or after the next group session, the Group Nutritionist arranges a time to call the participant. The Group Nutritionist uses the phone call to review the session materials, including completion of the Home Activity Worksheet assignments, and verbally collects self-monitoring data. The Group Nutritionist also uses the phone call to respond to participant questions and discuss ongoing challenges.

Note: The telephone make-up method should be used only when it is not possible to see a participant in an individual meeting.

Participant Misses Three or More of First Six Sessions

If a woman misses three or more of the first six weekly sessions, the Group Nutritionist uses <u>one</u> of the following methods:

- Encourages the woman to begin again with a new group in order to complete the basic skills needed to change her eating patterns.
- Arranges an individual meeting with the participant if it is not possible or acceptable for the woman to begin a new group. The individual meeting can be used to review a maximum of three DM Intervention sessions.

Participant Misses Three Consecutive Sessions After the First Six Weeks

If a woman misses three consecutive sessions after the first six weeks, the Group Nutritionist uses the following procedure:

- Schedules an individual meeting with the participant. The Group Nutritionist reviews all the worksheets from the missed sessions, responds to the participant's questions and discusses ongoing challenges. In addition, the Group Nutritionist collects all available self-monitoring data that is missing from the previous DM Intervention sessions. A maximum of three missed sessions can be covered during one individual visit.

6.10.5.3 Data Collection for Women Who Miss Sessions (Required)

The Group Nutritionist records session data for make-up activities on the *Form 63 - Session Data Sheet* or *Form 64 - Individual Data Sheet,* as described below. Refer to *Vol. 3 - Forms* for detailed instructions on the completion of these two forms.

Participant Attends Another Group

If a participant attends another group's session(s), the Group Nutritionist uses the following procedures:

- Attaches the participant's barcode label to the *Form 63 - Session Data Sheet* of the group she attends.
- Records the participant's session data (attendance, scores, score source and home activity completion) on *Form 63* of the group she attends.

Participant Meets Individually with Group Nutritionist

If a participant meets individually with the Group Nutritionist (in person or by telephone), the Group Nutritionist uses the following procedures:

- Records the participant's session data on a *Form 64*.
- Completes a *Form 64* for each session covered during the individual visit. For example, if the Group Nutritionist meets individually with a participant to make-up three missed sessions, she/he would complete three separate *Form 64* forms.

6.10.6 Determining and Maintaining Levels of DM Intervention Participation (Required)

6.10.6.1 Participation Goals

The goals of DM Intervention participation are to:

- Start DM Intervention (regular group session attendance/completion) as soon as possible.
- Keep women participating in the DM Intervention at the highest level possible.
- Resume participation as quickly as possible, if DM Intervention is interrupted.
- "Stop DM Intervention" (Form 7) only if necessary.

DM Dietary Change participants are an important part of the Dietary Modification Clinical Trial whether they are active participants of a Dietary Change group or "Awaiting DM Intervention Start-Up". Once a participant has been randomized into DM, her data (or lack of data) will be included in study analyses, regardless of her participation and/or performance. This "once randomized, then analyzed" concept is the reason for the emphasis on getting Dietary Change participants into groups as soon as possible and keeping them in groups whenever possible. However, there may be occasions when a woman is unavailable or unwilling to participate in a group. To handle these special situations, the Group Nutritionist should use the procedures described in *Section 6.10.8 – Interrupted DM Intervention Participant Procedures* and shown in *Figure 6.2 - Interrupted DM Intervention Participation Flow.*

6.10.6.2 Definition of Non-Participation and Active Participation

Participation in the DM Intervention can be defined as Non-Participation or Active-Participation. The Group Nutritionist makes every attempt to encourage Active Participation.

6.10.6.2.1 Non-Participation

A Dietary Change participant is classified as a non-participant if she refuses all contact (in-person, by phone, or by mail) with the Group Nutritionist and other CC nutrition staff, and all special retention activities have failed. Refer to *Vol. 2, Section 17.2.3* (including all subsections) – *Special Activities for DM Intervention Retention Challenges* and *17.4 - Changes in Participant Status*.

6.10.6.2.2 Active-Participation

A Dietary Change participant is classified as an active participant if she is completing any of the activities described below.

Full participation:

- The participant is attending Dietary Change group sessions (and/or completing session makeup activities).

Low participation:

- The participant is unable or unwilling to attend Dietary Change group sessions or complete session makeup activities, but agrees to have contact with the Group Nutritionist or other CC nutrition staff as described in *Section 6.10.8 – Interrupted DM Intervention Participation Procedures.*

6.10.7 Triage System for DM Intervention

The Triage System for DM Intervention assists Nutritionists in case management and setting priorities. The system divides active Dietary Change participants into one of four adherence categories based on participant session completion and self-monitoring effort. Level 1 reflects high adherence and Level 4 reflects low adherence. The Triage System for DM Intervention provides a mechanism for prioritizing nutritionist effort according to participant level of effort.

6.10.7.1 Participant Level of Effort

Participant level of effort can be generally be described as follows:

- The Level 1 participant completes sessions, self-monitors, and meets fat gram goal.
- The Level 2 participant completes sessions, self-monitors, but does not meet fat gram goal.
- The Level 3 participant completes sessions, but does not provide fat scores.
- The Level 4 participant does not complete sessions (and seldom, if ever, provides fat scores).

Refer to Table 6.2 - *Triage System for DM Intervention* for a complete summary of the specific session completion and self-monitoring criteria defining each level.

Table 6.2
Triage System for DM Intervention

Adherence Level	General Description of Participant Effort	Criteria
Level 1 (High)	Completes sessions, self-monitors, and meets fat gram goal.	During the previous 12 months, the participant: • completed ≥ 50% of sessions, • provided a fat score at ≥ 50% of sessions, • the average of the provided scores was at or below fat gram goal.
Level 2 (Medium)	Completes sessions, self-monitors, but does not meet fat gram goal.	During the previous 12 months, the participant: • completed ≥ 50% of sessions, • provided a fat score at ≥ 50% of sessions, • the average of the provided scores was above fat gram goal.
Level 3 (Medium)	Completes sessions, but does not provide fat scores.	During the previous 12 months, the participant: • completed ≥ 50% of sessions, • provided a fat score at < 50% of sessions.
Level 4 (Low)	Does not complete sessions (these participants seldom, if ever, self-monitor).	During the previous 12 months, the participant: • completed < 50% of sessions.

6.10.7.2 Nutritionist Level of Effort

Nutritionists triage efforts beginning with participants in Level 1 and ending with participants in Level 4. Nutritionists generally spend the most time applying high intensity effort to participants in Level 2 and Level 3, and relatively less time applying low intensity effort to participants in Level 1 and Level 4. The actual amount of time devoted to efforts within each level depends on DM adherence and CC resources. Clinical Centers with high staff resources and high DM adherence may have the opportunity to apply high intensity efforts to all adherence levels. Clinical Centers with low staff resources and low DM adherence rely on the Triage System for DM Intervention to prioritize nutritionist efforts.

Refer to *Section 6.10.8 – Interrupted DM Intervention Participation Procedures* for information about using the Triage System for DM Intervention to guide low intensity efforts with Level 4 participants, i.e., active participants who are unable or unwilling to attend Dietary Change group sessions or complete makeup activities, but agree to have contact with the Group Nutritionist or other CC nutrition staff.

Refer *Section 6.11 – Intensive Intervention Protocol (IIP)* for information about using the Triage System for DM Intervention to guide high intensity efforts of the Intensive Intervention Protocol.

6.10.8 Interrupted DM Intervention Participation Procedures

Participants with low DM Intervention participation have Level 4 adherence per the Triage System for DM Intervention. These are participants who are unable or unwilling to attend Dietary Change group sessions or complete makeup activities, but agree to have contact with the Group Nutritionist or other CC nutrition staff. Refer to *Sections 6.10.6.2.2. – Active Participation* and *6.10.7.1 – Participant Level of Effort.*

Nutritionists triage efforts by using low intensity Interrupted DM Intervention Participation Procedures with Level 4 participants. Refer to *Figure 6.2 - Interrupted DM Intervention Participation Flow*.

If CC resources support focusing higher intensity effort on Level 4 participants, the nutritionist uses procedures outlined in *Section 6.11 – Intensive Intervention Protocol*.

6.10.8.1 Awaiting Start-up of DM Intervention

During Recruitment

After a participant is randomized into the DM Intervention, the goal is to have her attending/completing sessions by three months (12 weeks) post-randomization, whenever possible. If a Dietary Change participant has not started Session 1 in a group by five months (20 weeks) post-randomization due to insufficient DM group formation at the CC, and not due to the participant's unavailability or unwillingness, the Lead Nutritionist should reassess the CC's group formation schedule.

Dietary Change participants who have not started DM Intervention (i.e., not completed Session 1 or more) should remain on the waiting list and should be contacted monthly using procedures described in *Section 6.8.2.3 – Handling DM Intervention Participants Waiting for a Group (Required)* until they start DM Intervention sessions. If a Dietary Change participant who has been on the waiting list for a long time expresses frustration or feels pressured by the required monthly contacts, keep her on the waiting list but negotiate a less frequent contact (e.g., quarterly). Avoid completing a *Form 7-Participation Status* to "stop" DM Intervention for participants on the waiting list, even if they remain on the waiting list for a long time.

The advantage of keeping a Dietary Change participant on the waiting list rather than completing a *Form 7-Participation Status* to "stop" DM Intervention, is that it:

- Allows the CC to track the individual participant and ensure that she is not lost in the shuffle of recruitment/screening activities.
- Maintains the Lead Nutritionist's awareness of the length of time a Dietary Change participant has been waiting to start Session 1.
- Maintains a stronger link between the CC and the Dietary Change participant, thus increasing the potential of actively involving the participant at a later date.

A Clinical Center's guiding principle should be to maintain contact with Dietary Change participants and negotiate the greatest amount of DM participation possible without having participants stop DM Intervention.

If a Dietary Change participant on the waiting list refuses all contact (in-person, by phone or by mail) with the Group Nutritionist and other CC nutrition staff, and all special retention activities have failed, refer to *Section 6.10.6.2.1 – Non-Participation.*

End of Recruitment

As the study reaches the end of recruitment and Lead Nutritionists plan final Dietary Change group formation, they may find they have participants who have not started DM Intervention and are unable/unwilling to attend sessions with either existing or currently forming final groups.

A Dietary Change participant who has not started DM Intervention and is unable/unwilling to attend sessions with either existing or currently forming final groups should be contacted to assess the situation and to determine willingness to continue active participation. Refer to *Section 6.10.8.2 – Assessing the Situation for Interrupted DM Intervention Participation*. If the participant is willing to continue active participation, assign her to an existing or currently forming final group. The group assignment decision should be based on maximizing the participant's exposure to and participation in the intervention and staffing considerations. Work with the participant to develop and implement a plan for delivering as much intervention as possible in as efficient a manner as possible. Refer to *Sections 6.10.8.3 – 6.10.8.6.*

Refer to *Section 6.8.2.4 - Final Group Formation at the End of Recruitment* for information about intervention start-up and final group formation options at the end of recruitment.

6.10.8.2 Assessing the Situation for Interrupted DM Intervention Participation

The Group Nutritionist assesses the situation when a Dietary Change participant who has started DM Intervention (i.e., completed Session 1 or more) completes less than 50% of sessions during the previous 12 months. The Group Nutritionist uses the *IIP Triage & Tracking* (WHIP0444) report to identify these participants. Refer to *Vol. 5 – Data System, Section 8.2 – DM Intervention Group Reports* and *Vol. 7, Section 5, Table 5.2 – CC Schedule for Data Monitoring – Required.* At this time, the Group Nutritionist contacts the

participant and assesses the situation. The key points to include when assessing the reasons for not completing sessions include the participant's perception of the problem as well as her preference for a plan. Refer to *Figure 6.3 – Interrupted DM Intervention Participation Worksheet*.

End of Recruitment

The Group Nutritionist assesses the situation when a Dietary Change participant has not started DM Intervention and is unable/unwilling to attend either existing or currently forming final groups. The key points to include in the assessment are the same as those outlined above for a participant who has started DM Intervention. Refer to *Section 6.10.8.1 – Awaiting Startup of Dietary Change* for additional information about handling participants who have not started intervention at the end of recruitment.

6.10.8.3 Developing and Implementing a Plan for Interrupted DM Intervention Participation

If after assessing the situation, the participant is willing to continue active participation, the Group Nutritionist and participant develop a plan and timeline to keep the participant involved and/or to resume regular group participation. The ultimate goal is to have Dietary Change women with interrupted participation resume regular group attendance. The key points to include when developing a plan to maintain active participation and/or contact are listed below. Refer to *Figure 6.3 - Interrupted DM Intervention Participation Worksheet*.

- Keep the participant assigned to an active Dietary Change group.
- Based on the participant's level of effort, determine: contact type, contact frequency, contact content, and date to reassess plan.

The Group Nutritionist encourages the woman to attend group sessions during her interrupted participation whenever possible. The woman may attend session(s) with her assigned group or with another group as a guest. Refer to *Section 6.10.5.3 – Data Collection for Women Who Miss Sessions.*

End of Recruitment

The Group Nutritionist develops a plan for maximizing exposure to and participation in the DM Intervention when an active Dietary Change participant has not started DM Intervention and is unable/unwilling to attend sessions with either existing or currently forming final groups. The plan includes all aspects described above for a participant who has started intervention, plus the following additional key points:

- Remove the participant from the waiting list by assigning her to an active Dietary Change group.
- Make every effort to have the participant complete at least Session 1.

Refer to *Section 6.10.8.1 – Awaiting Startup of DM Intervention* for additional information about handling participants who have not started intervention at the end of recruitment.

6.10.8.4 Documenting and Tracking Interrupted DM Intervention Participation Plan and Contacts

Interrupted DM Intervention Participation Worksheet (Figure 6.3)

Use the *Interrupted DM Intervention Participation Worksheet (Figure 6.3),* a similarly designed CC-developed worksheet, or the participant progress notes to document the following key points of the plan:

- Contact: type, frequency and content.
- Date to reassess plan and revise if appropriate.

Form 24 – Adherence and Retention Worksheet

Form 24 – Adherence and Retention Worksheet is recommended for use when clinical center staff have made a contact to conduct special retention activities with participants. Refer to *Vol. 3 – Forms, Instructions for Form 24 – Adherence and Retention Worksheet.*

The Group Nutritionist is strongly encouraged to use *Form 24 – Adherence and Retention Worksheet* to document all Interrupted DM Intervention Participation contacts. Per this recommendation, *Form 24 – Adherence and Retention Worksheet* would be completed for the following contacts:

- When Interrupted DM Intervention Participation procedures are initiated (i.e., when the Group Nutritionist contacts the participant to assess the situation and develop a plan).
- When the participant is contacted per the Interrupted DM Intervention Participation plan.

Using *Form 24 – Adherence and Retention Worksheet* allows the Group Nutritionist to track Dietary Change participants receiving retention contacts (i.e., Interrupted DM Intervention Participation). The *IIP Triage & Tracking* (WHIP 0444) report lists the re-contact date from the *Form 24* most recently completed for DM Intervention Participation (Qx. 6.3). Refer to *Vol. 5 –Data System, Section 8.2 – DM Intervention Group Reports*. The *Member Adherence and Retention Activity Tracking* (WHIP 1238) report shows additional information from *Form 24*. Refer to *Section 17.2.1 – Identifying Retention Challenges and Tracking Special Activities* and *Vol. 5 – Data System, Appendix B3.4 – Adherence and Retention Worksheet*.

Progress Notes

The Group Nutritionist is strongly encouraged to place a note in the participant progress notes to cross reference the completion of any *Form 24 – Adherence and Retention Worksheet*, if this form is used to document participant contacts. This cross referencing will help other Group Nutritionists (e.g., replacement or relief staff) track Interrupted DM Intervention Participation activities.

6.10.8.5 Reassessing the Interrupted DM Intervention Participation Plan

The Group Nutritionist reassesses the situation at the time outlined in the Interrupted DM Intervention Participation plan.

Participant resumes group session attendance/completion

If a woman resumes regular group session attendance after a period of Interrupted DM Intervention Participation, the Group Nutritionist uses the following guidelines (listed in order of priority) for triaging participant and staff effort:

- Encourage the participant to focus on maintaining the newly resumed session attendance and self-monitoring.
- Encourage the participant to self-monitor, if not resumed.
- During Year 1, complete missed sessions if the participant is willing and local staffing configurations support this level of effort. Encourage participants to do makeup sessions by guest attendance whenever possible. Complete individual makeup only if group makeup is unavailable and the participant is willing to complete the session individually.
- During Maintenance, do not complete missed sessions that cannot be completed by guest group attendance.

Participant does not resume group session attendance/completion

If a woman does not resume group session attendance/completion at the agreed upon time, use the same procedures as described above in *Sections 6.10.8.2 – Assessing the Situation for Interrupted DM Intervention Participation* and *6.10.8.3 – Developing and Implementing a Plan for Interrupted DM Intervention Participation* to reassess the participant's situation and plan for continued contact. Document and track any revisions to the plan using the procedures described in *Section 6.10.8.4 – Documenting and Tracking Interrupted DM Intervention Participation Plan and Contacts.*

6.10.8.6 Handling Participants Who Refuse Contact with the Group Nutritionist and Other CC Nutrition Staff

The Group Nutritionist uses the procedures described in *Section 6.10.6.2.1 – Non-Participation* if a Dietary Change participant refuses contact (in person, by phone, or by mail) with the Group Nutritionist and other CC nutrition staff.

Figure 6.2
Interrupted DM Intervention Participation Flow

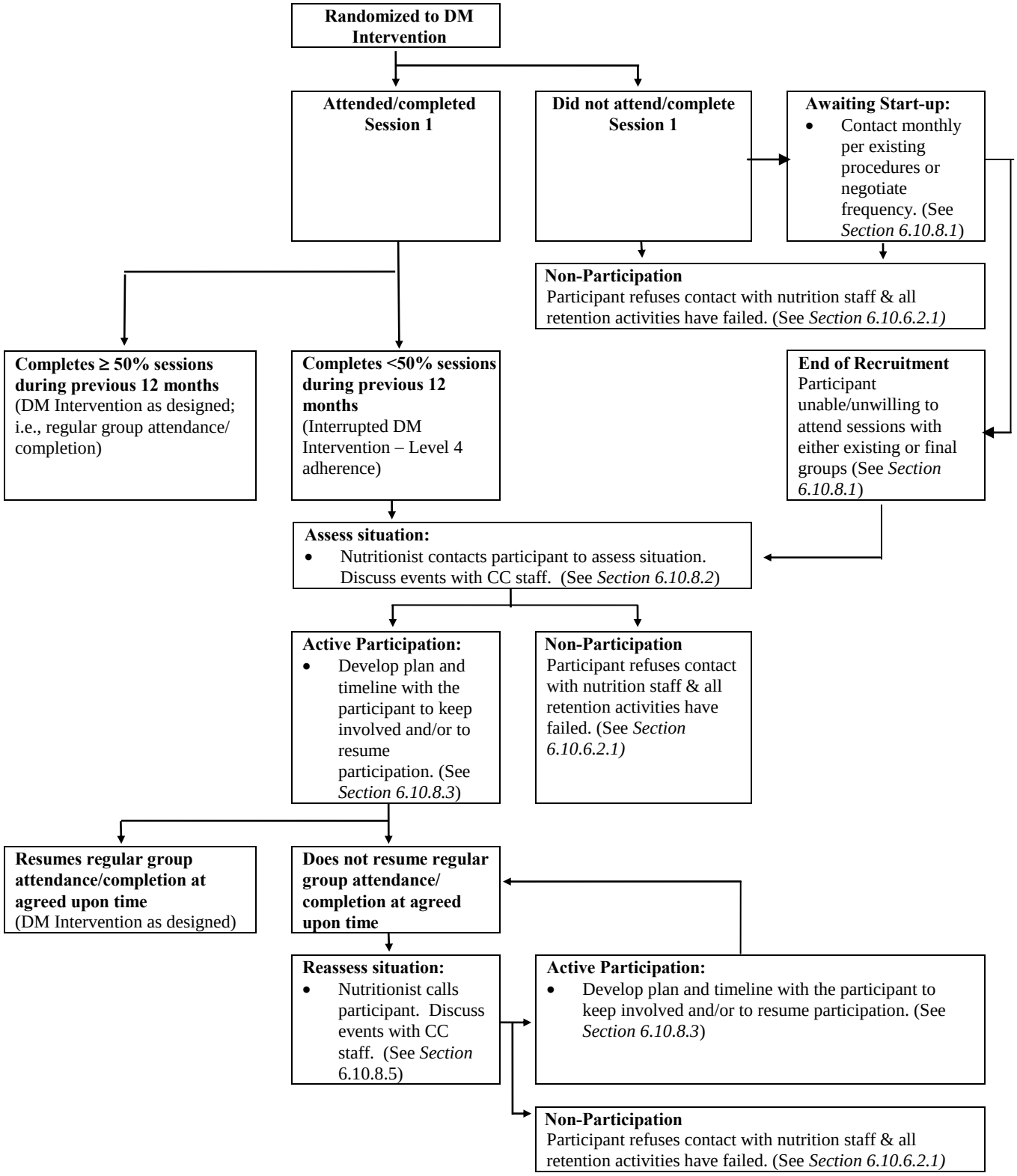

Figure 6.3
Interrupted DM Intervention Participation Worksheet

Participant Name/ID: _____	**Group Nutritionist: _____**
Participant Phone: _____	**Group Number: _____**

Date: _____

Assessment:

Participant has completed less than 50% of sessions during previous 12 months (Level 4 adherence).

_____
_____
_____
_____
_____
_____
_____

Goal:

Maintain contact during interrupted intervention and resume group session attendance.

_____
_____

Plan:

- Keep participant assigned to an active Dietary change Group.
- Contact Type: _____
- Contact Frequency: _____
- Contact Content: _____
- Date to reassess plan (see Form 24): _____
- _____
- _____

6.11 Intensive Intervention Protocol (IIP) (Required)

The Intensive Intervention Protocol (IIP) is a protocol composed of three individual contacts using a brief motivational interviewing approach. The goal of the IIP is to increase the C- I difference by helping participants discover their own motivation to consider dietary changes. The timeline for completing the initial round of IIP contacts is December 31, 2000.

6.11.1 IIP Sample (Who To Contact)

All DM Intervention participants (Year 1 and Maintenance) are eligible for IIP. The IIP sample for each Clinical Center is based on the Triage System for DM Intervention. This system categorizes participants into one of four adherence levels based on a participant's session completion and self-monitoring efforts. Refer to *Section 6.10.7 – Triage System for DM Intervention*.

Nutritionists should focus first on participants triaged to Levels 2 and 3. This focus provides Nutritionists an opportunity to tailor adherence efforts to participants' efforts and abilities. The participants in Levels 2 and 3 represent a cohort of participants who are currently participating in the WHI Intervention but are not meeting their fat gram goal or not self-monitoring. IIP contacts may be expanded to other participants after completing the IIP contacts with participants in Levels 2 and 3.

The Nutritionist has discretion when deciding whether or not to conduct IIP contacts with individual participants. Per clinical judgement, the Nutritionist may decide not to conduct IIP contacts with participants who are in crisis situations (e.g., serious personal or family illness, death of spouse, etc.). However, it is critically important to keep in mind that every time a decision is made not to do an IIP contact with a participant, WHI misses an opportunity to improve the C-I.

6.11.2 Number, Type, and Frequency of Contacts

The following section presents information about the usual number, type and frequency of IIP contacts.

Number of Contacts.

The IIP will most often be a series of three contacts. Occasionally a participant will receive more or fewer than three contacts based on Nutritionist discretion.

Type of Contact.

IIP contacts will most often be a mixture of in-person and telephone contacts as follows:

- Contact to schedule IIP Contact #1- usually by telephone. Refer to *Scheduling IIP Contact #1 – Sample Script – Figure 6.4*.
- IIP Contact #1 - usually in-person.
- IIP Contacts #2+ - usually by telephone.

This format provides a mix of rapport building (in-person) and efficient (telephone) contacts. However, if the IIP Contact #1 cannot be done in person, it would be preferable for the Nutritionist to conduct the contact by telephone than to not complete the contact at all.

Frequency of Contact.

Most IIP contacts will be spaced about one month apart. The Nutritionist will most often initiate and complete the series of IIP contacts within 3 months. Completing the series in this timeframe will facilitate sample management. Refer to *Vol. 2, Section 6.11.6. - IIP Sample Management*.

Figure 6.4

Scheduling IIP Contact #1 - - Sample Script

Hello Mrs. _____. This is ____from WHI. Do you have a few minutes? I'm calling today because I'm interested in hearing about how WHI is going for you and also to share some information about the Dietary program.

As you know from your group sessions, we are finding that the study participants, as a whole, are not decreasing their fat intake enough to answer the questions asked by the research. We're also finding that many women are getting burned out and tired. Some women who made a lot of changes at first are finding it very difficult to keep them up.

Because of this, we've added something new to the Dietary Change program. We are contacting participants to set-up individual meetings (with a nutritionist). We're hoping that by talking with women, like yourself, we can get a better picture of what is really happening. We need know how WHI is going - - what you are experiencing. Our hope is to find ways to help our participants and the study move closer to the goal.

We need your help to do this. Can we schedule an in-person meeting to talk about how WHI is going for you? How would ___ work for you?

6.11.3 Framework of the Contact

The Nutritionist uses a brief motivational interviewing approach to conduct the IIP contacts. The approach is a participant-centered method for increasing participants' motivation to consider dietary changes and to negotiate the best course of action.

During the contact, the Nutritionist does not assume an authoritarian role. She/he attempts to draw on and enhance the participant's internal motivation to make eating behavior changes based on the participant's own decisions and choices. The focus shifts from giving information, advice and behavior change prescriptions to helping the participant explore concerns, ambivalence, reasons for change, and ideas and strategies for change. The Nutritionist utilizes a variety of negotiation strategies based on the participant's readiness to consider change.

The IIP Roadmap provides the structure to guide the Nutritionist through an IIP contact. Refer to *Figure 6.5 - IIP Simple Roadmap* and *Figure 6.6 - IIP Detailed Roadmap*. The Simple Roadmap provides an overview of the components, while the detailed version of the IIP Roadmap provides suggested script and questions for each of the components. The components of the IIP Roadmap include:

- Set the Stage
- Provide Feedback
- Assess Readiness to Make WHI Dietary Changes
- Offer Support (Optional Additional Strategies)
- Close

Although the steps in the IIP Roadmap are listed in the order shown above, the contact does not need to flow in this exact order. For example, a Nutritionist may opt to assess a participant's readiness to make dietary changes before providing feedback.

The theoretical background, goals, key elements, areas to avoid, key questions/statements, strategies and tools for each component are provided in the IIP training manual. Refer to *Vol. 2, Appendix G.5 – Motivation Enhancement Training August 1999, WHI Intensive Intervention Protocol*.

The Nutritionist provides participants with individualized feedback about self-monitoring and session completion efforts by using information from *the Individual Progress Report* (*WHIP 0428*), or by creating graphs using the WHILMA Custom Data Extract System. Refer to *Vol. 5 – Data System.*

Figure 6.5

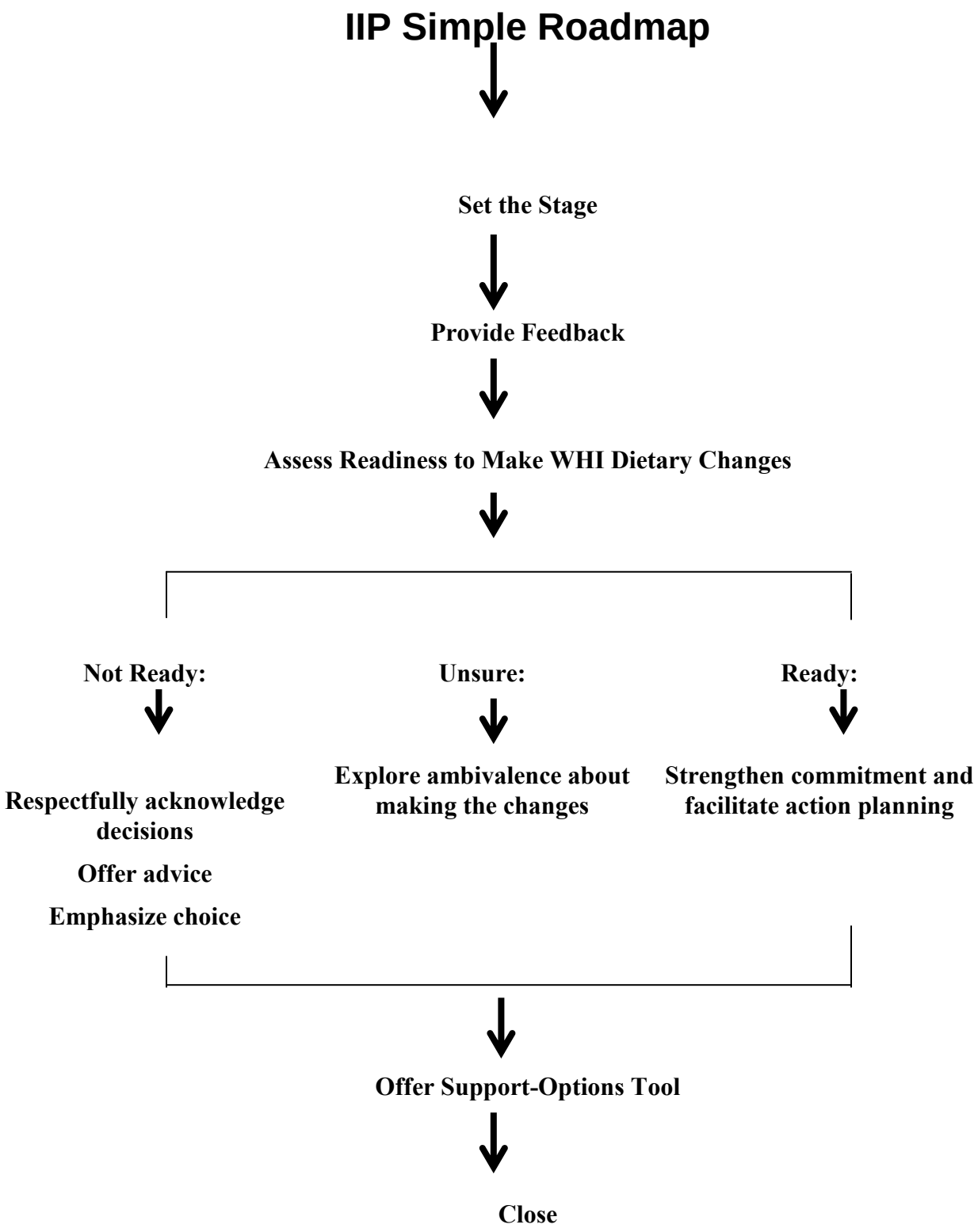

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Figure 6.6

WHI IIP Detailed Roadmap

Set the Stage

- **Establish Rapport.**
- **Make Opening Statement**. Let the participant know who you are (if needed), why you are there, and how much time you have.
- **Ask permission to discuss participation in the study.**

We have about _____ minutes to meet today. I thought we might talk about your participation in WHI and how the study is going for you. I have some information and feedback that I'd like to share but mostly I want to understand how you are doing with the study. Would that be all right?

Provide Feedback

- **Provide feedback in a neutral manner; compare with norms and standards.**
- **Elicit participant's interpretation.**

"As you probably know from the quarterly sessions, one of things we are finding is that the study participants, as a whole, are not decreasing their fat intake enough to answer the questions asked by the research. (Show graph if appropriate) We're also finding that many women are getting burned out and tired. Some women who made a lot of changes at first are finding it very difficult to keep them up. We expected some of that but have concerns about how much trouble some participants are having. We're hoping that by talking with women like you we can get a better picture of what is really happening, and we hope to find some ways to help our participants and the study move closer to the goal."

***"**What are your thoughts and feeling about this?"*

"What do you think about this?"

"I also have your latest Individual Progress report here and the graph that shows how your group is doing compared to all other groups at our center and the study as a whole over time. What do you think of this information?" "Do these data make sense to you?"

For participants who have been self-monitoring:
"Your average daily fat gram intake is ___. Does this seem right to you? How closely do the days you self-monitor represent what you typically eat?"

For participants who have not been self-monitoring:
"I don't have your current food records so I am wondering, when you think about your typical day, how would you say your fat gram intake compares with your fat gram goal? How has it changed?"

"In general, how is WHI going for you."
"Given all the complexities, how does your participation in WHI fit into your life?"

- **Listen and summarize. Emphasize self-motivational statements.**

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Figure 6.6 (continued)

Assess Readiness to make WHI Dietary Changes

"I really appreciate you sharing your thoughts and feelings with me. I do believe it will help the study. In order to best make use of our time today I'd like to ask you a question."

- **Show ruler:**

"On a scale of 0-12, Where would you say your motivation / energy / enthusiasm / interest is for following the dietary recommendations that WHI has asked you to follow?" (0 = not at all interested; 12 = very interested and motivated to follow all the recommendations)

- **Explore participant's selection:**

Straight question: *"Why did you pick a _____?"*

Backward questions: *"Why did you pick a 4 and not a 1?"*

Forwards question: *"What would need to be different in your life to move from a 2 to an 8?"*

- **Listen and summarize. Emphasize self-motivational statements.**

If not ready:	**If unsure:**	**If ready:**
Respectfully acknowledge decisions. **Key Questions:** *"I wonder what would have to be different for you to consider making any changes?"* **Listen and summarize.** **Offer advice and emphasize choice:** **"***I understand and respect your decisions about WHI right now. Of course, I encourage you to think about making the dietary changes when the time is right for you. A diet low in fat and high in fruits, vegetables and grains may reduce your risk of diseases such as cancer and heart disease. Also, your participation in the study is important to the results. It is your choice and I'm confident that if you chose to make any changes you can find a way to be successful in the long term."*	**Explore ambivalence about making the changes** **Key Questions**: *"What are the advantages/disadvantages of making dietary changes?"* *"What do you like/dislike about the WHI dietary changes*?" **Listen and summarize.** *"Where does that leave you?"* *"What do you see as the next step?"*	**Strengthen commitment.** **Facilitate action planning.** **Key Questions**: *"What are your reasons for wanting to make or maintain these changes?"* *"What are you thinking about doing?"* *"What have been your successes with this in the past?"* *"What works for you when making changes?"* **Listen and summarize.** **Help participant set a reasonable plan of action.**

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Figure 6.6 (continued)

Offer Support (Optional Additional Strategies)

For participants who are unsure or ready*:* "Here are some strategies that some participants have found helpful when thinking about the possibility of change. (show How Can We Support You option tool) Are you interested in exploring any of them? Or is there something else that might be more helpful?"

For participants who are not ready: "I understand that you are not interested in making any changes right now. We still have about 20 minutes today and I'd like to use that time in a way that is best for you. Here are some discussion items that some participants have found helpful when thinking about their participation in WHI. Are any of these of interest to you or is there something else you would like to discuss this time?"

Assess current eating behavior.

Tell me about a typical day in regard to food.
What do you see as ideal eating habits? Where would you like to be?

Explore options for dietary change (WHI Dietary Goals options tool).

Here are the WHI dietary goals. What do you think about them?
Which of these goals might you be interested in working on right now?

Explore study activities (WHI Study Activities options tool).

Here are some of the WHI activities. What do you think about them?
What has changed for you since the beginning?

Explore self-monitoring.

What are your thoughts about self-monitoring?
What are the advantages/disadvantages of self-monitoring?

Explore barriers to change

What do you see as your greatest barriers to change?
What kinds of strategies have you used to overcome barriers?

Dreaming.

Let's suppose that it is 10 years from now. WHI is over. With the help of all the participants we were able to prove that making dietary changes reduced the risk of cancer and heart disease What is your life like?

Closing

- **Summarize the session, including thoughts and concerns.**
- **Support self-efficacy.**
- **Thank the participant.**
- **Arrange follow-up contact**

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6.11.4 Documenting IIP Contacts

The Nutritionist uses *Form 64 – Individual Data Sheet (ver. 4)* and progress notes to document IIP contacts.

Form 64.

Form 64 – Individual Data Sheet (ver. 4) is the data collection form that documents who, when, how, and how much IIP a participant receives. The Nutritionist must complete a *Form 64* for each IIP contact. Questions 5, 9 and 10 pertain to IIP data collection.

The goals of *Form 64 - Individual Data Sheet (ver. 4)*, Qx. 5 – Description of contact are:

- To document who receives the Intensive Intervention Protocol (IIP) (Qx. 5, boxes 26-29);
- To document who does not receive IIP (Qx 5, boxes 24-25), and;
- If a participant does not receive IIP, to identify whether this is due to:
  - Nutritionist discretion (Qx. 5, box 24 -Not appropriate for IIP), or
  - Participant request (Qx. 5 box 25 -Participant declined IIP).

Below are examples of how to complete *Form 64*, Qx. 5 in various situations. For complete details and instructions, refer to *Vol. 3 – Forms, Instructions for Form 64 – Individual Data Sheet (ver. 4)*.

- *Not appropriate for IIP*: The Nutritionist marks *Form 64* - Qx. 5, box 24 "Not appropriate for IIP" when her/his clinical judgement indicates that a participant should not be approached for IIP. This decision may occur because a participant has a crisis situation (e.g., serious personal or family illness, the death of spouse, etc.). If the Nutritionist wants to try to initiate IIP at a later date, she/he may complete Qx. 9 "Date to re-contact". Note: Qx. 5, box 24 "Not appropriate for IIP" should only be used if a participant does not receive any IIP. Therefore, once a participant has received IIP Contact #1, Qx. 5, box 24 should not be used.
- *Participant declined IIP: The* Nutritionist marks *Form 64* - Qx. 5, box 25 "Participant declined IIP" if a participant declines IIP Contact #1 when approached. If the Nutritionist wants to try to initiate IIP at a later date, she/he may complete Qx. 9 "Date to re-contact". Note: Qx. 5, box 25 "Participant declined IIP" should only be used if a participant does not receive any IIP. Therefore, once a participant has received IIP Contact #1, Qx. 5, box 25 should not be used.
- *IIP Contact 1-4+: For* all other IIP contacts (i.e., IIP Contact #s: 1, 2, 3, or 4+), the Nutritionist selects the appropriate box on *Form 64* – Qx. 5 to document the IIP contact. In addition, she/he records the date for the next scheduled IIP contact (Qx. 9), if appropriate.
- *IIP Complete:* The Nutritionist marks Qx. 10 "IIP Complete" on *Form 64* when clinical judgement indicates that the IIP series is complete (i.e., no more IIP contacts will be done before December 31, 2000). The Nutritionist most often marks "IIP Complete" after IIP Contact #3. However, the Nutritionist has the discretion to mark "IIP Complete" following IIP Contact #s 1 - 4+.

Progress Notes.

In addition to *Form 64 – Individual Data Sheet (ver. 4)*, Nutritionists will want to keep notes about each IIP contact. The purpose of these IIP progress notes is to help the Nutritionist manage contact information that is not data-entered, but is important for conducting future IIP contacts [e.g. the participant's interpretation of the feedback discussed; how the participant responded to readiness question(s); self-motivational statements]. Keeping notes is required; the method used to keep the notes is the Nutritionist's option. [Refer to *Figure 6.7 – IIP Progress Notes* (*Example*)]

Figure 6.7

IIP Progress Notes (Example)

Participant Name/ID:_____ Group Nutritionist: _____

Participant Phone: _____ Group Number: _____

Date: _____ **Contact #: _____**

Feedback Discussion	**Self-Motivational Statements**
Feedback provided: Ppt's interpretation:	Problem Recognition: Concern:
Readiness Assessment	
Readiness question(s) asked: Ppt's response: ___ on a scale of ____ to ____	Intention to Change:
Intervention Approach	
Check one: ___ Not Ready ___ Unsure ___ Ready	Optimism:
Support Offered/Options Explored	**Action Plan (if ready)**

Next Steps/Follow-up Contact:

6.11.5 Tracking IIP Contacts

The *IIP Triage & Tracking* (WHIP 0444) report is a WHILMA-based report that the Nutritionist uses to manage local implementation of IIP. The report includes all active Dietary Change participants assigned to a DM group. For each participant listed, the report shows several key IIP tracking variables (e.g., Nutritionist, DM Group, Triage Level, % Fat Goal Overall, most recent IIP Contact and Date, Date to Re-contact and IIP Complete).

The Lead Nutritionist (or designee) uses the *IIP Triage & Tracking* (WHIP 0444) report to manage the IIP sample for the clinical center. The report will:

- Categorize all active Dietary Change participants by triage level.
- Identify the IIP sample (participants triaged to Levels 2 and 3).
- Track description and date of most recent IIP contact for each participant.
- Track IIP re-contact dates.
- Track participants who have completed IIP.

The report lists participants in order by Nutritionist, DM Group, Triage Level, and last name. The Triage Level and % Fat Goal Overall are based on a 12-month assessment period (12 months prior to the report run date). For example, if a Nutritionist runs the report on 11/1/99 (if DM Snapshot updated on 11/1/99), the report would be based on the twelve month assessment period between 11/2/98 and 11/1/99. Because the report is based on data from the last 12 months, it is critical for a CC to maintain timely DM Intervention data entry.

It is recommended that Nutritionists run the *IIP Triage & Tracking* (WHIP 0444) report quarterly from the CC local database (see *Section 6.11.6 - IIP Sample Management).* For complete details about running the *IIP Triage & Tracking* (WHIP 0444) report, refer to *Vol. 5, Section 8.2 – DM Reports*

6.11.6 IIP Sample Management

The Lead Nutritionist develops and implements an IIP Sample Management Plan.

Development of Plan:

It is the responsibility of the Lead Nutritionist to develop an IIP Sample Management Plan. The purpose of this plan is to provide guidance for the CC in completing the first series of IIP contacts by the studywide timeline - December 31, 2000. In developing a plan, the Lead Nutritionist includes the following considerations:

- Time blocks available for contacts (divide into manageable blocks of time; suggest 3-month blocks).
- Total IIP sample estimate.
- Percent of IIP sample to see per time block.
- Projected number of participants to see per time block.
- Projected number of contacts to make per time block. (Assume that each participant will receive a series of 3 contacts approximately 1 month apart).

The table below provides an example using an estimated IIP sample of 200 participants.

Time blocks available (3-month).		Oct-Dec 1999	Jan-Mar 2000	Apr-June 2000	July-Sept 2000	Oct-Dec 2000
Estimate total IIP sample (Levels 2&3)	200					
Percent of IIP sample to see per time block.		10%	35%	30%	25%	0%
Project # of participants to see per time block.	IIP sample estimate multiplied by % to see per time block.	200 x .10 = 20	200 x .35 = 70	200 x .30 = 60	200 x .25 = 50	
Project # of contacts per time block (assume a series of 3 contacts/participant).	Number of participants to see per time block multiplied by 3.	20 x 3 = 60	70 x 3 = 210	60 x 3 = 180	50 x 3 = 150	

When making a plan, the Lead Nutritionist also needs to consider some of the following:

- Number of nutritionists (or other trained staff) available to conduct contacts (e.g., workload distribution, part-time staff, vacations, etc.).
- Travel time and maximum efficiency for off-site locations. For example:
  - If going to an off site location, prioritize all participants in IIP sample who live or attend groups in the specific area. This may mean that the Nutritionist(s) conducting the IIP contacts may see participants who are not members of groups they facilitate.
- Availability of participants during extended holiday periods and/or winter travel.

Implementation of Plan:

Time Block #1:

1. October 1999: Run the *IIP Triage & Tracking* (WHIP 0444) report to identify the current (i.e., as of the report run date) total IIP sample for your CC.
2. Determine the number of participants to begin IIP during the first time block by multiplying the total IIP sample by the percent to be seen during the first time block.

   For example: If the total IIP sample is 200 and your plan is to begin 10% during this time block, then you need to begin IIP with at least 20 participants (200 x .10 = 20) during this time block.
3. Select participants who will begin IIP during this time block.
4. Conduct contacts. Conduct all IIP Contact #1s for the selected participants during the first month of the time block. Complete IIP for these participants within this time block by conducting all IIP Contacts #2, #3, and #4+ during the remainder of the time block.

   For example: If you plan to begin IIP with 20 participants during the time block, then you will make approximately 60 contacts (20 participants x approximately 3 contacts/participant) to complete IIP for these participants during the time block.

Time Block #2+:

1. Run the IIP *Triage & Tracking* (WHIP 0444) report early during the last month of each time block to identify the updated IIP sample for the next time block.

   For example: If the second time block is January-March, then run the *IIP Triage & Tracking* (WHIP 0444) report in early December. This will allow adequate time to complete data entry for the Fall Maintenance session (which should be finished by the end of November) and time to call and schedule IIP contacts for January through March.

2. Determine the number of participants to begin IIP during the time block by multiplying the updated total IIP sample by the percent assigned to the time block.

   For example: If the updated total IIP sample is 180 and your plan is to begin 35% during this time block, then you need to begin IIP with at least 63 participants (180 x .35 = 63) during this time block.

3. Select participants who will begin IIP during this time block. Select participants who have not had any IIP contacts.

   For example: The 63 participants to begin IIP during the January – March time block would be selected from the list of participants who do not have any IIP contacts showing on the *IIP Triage and Tracking* (WHIP0444) report.

4. Conduct contacts. Conduct all IIP Contact #1s for the selected participants during the first month of the time block. Complete IIP for these participants within this time block by conducting all IIP Contacts #2, #3, and #4+ during the remainder of the time block.

5. Repeat steps 1-4 for each time block.

The implementation plan described above assumes a non-staggered approach for initiating IIP Contact #1 during each time block (i.e., all IIP Contact #1s for the time block happen during the first month of the time block). Conducting all IIP Contact #1s during the first month of the time block means that most of the participants selected to begin IIP during the time block will also complete IIP within the time block.

Clinical Centers have the option to use a staggered approach for initiating IIP Contact #1 (i.e., the IIP Contact #1s for the time period are spread out during the first, second, and third month of the time period). Staggering the IIP Contact #1s throughout the time block means that most of the participants selected to begin IIP during the time block will not complete IIP until the next time block. Clinical Centers using a staggered approach for initiating IIP Contact #1s will need to see a larger percent of their total IIP sample during the earlier time blocks to allow time to conduct a larger percent of IIP Contacts 2+ in later time blocks. The staggered approach for initiating IIP Contact #1 also requires more complex tracking because each time block (except the first) will include participants beginning IIP during that time block plus participants from the previous time block who have not yet completed IIP.

Prioritizing IIP Contacts:

The Nutritionist considers participant requirements and availability when making decisions about which IIP-eligible participants to see first. For example:

- Prioritize participants who are leaving the area for extended periods (e.g., snowbirds, long vacation trips).
- Accommodate participants who need evenings or weekend contact times.
- Conduct IIP contacts by telephone, when participants are unable or unwilling to come to the CC (e.g., due to weather, transportation, health, etc.).

Scheduling Tips for IIP Contact #1:

Other areas that a Nutritionist needs to consider when contacting participants to schedule IIP Contact #1:

- Call easy to reach participants first.
- If a participant is not available and there is no answer, leave a brief message.
- If you reach a participant and she indicates that it is not a good time, schedule a 'call back.' Then make every effort to contact the participant at the agreed upon date and time.
- For IIP Contact #1, develop a tickler file (by contact date) to facilitate reminder calls or postcards.

6.11.7 IIP Evaluation

The FFQ will be used to evaluate the IIP. It is important to remember that the efficacy of the IIP protocol was tested in the IIP pilot study. Therefore, the IIP evaluation has the following objectives, in order of importance:

- Provide feedback on the effect of the IIP on the C-I difference for the purpose of intervention planning for the trial.
- Monitor completeness of the protocol implementation at the clinic level.

It is critical that the IIP intervention remains independent from its evaluation and that neither staff nor participants directly connect this new protocol with the monitoring instrument. Therefore, to minimize the potential for introducing intervention associated bias in FFQ responses, IIP contacts should not generally be scheduled in relation to the participant's annual visit. Some exceptions exist, such as for participants who live long distances from the clinical center or for whom travel to the clinical center is difficult. The data analyses program will be able to determine, for any Dietary Change participant completing an FFQ, whether (and when) she received the IIP intervention.

6.12 Maintenance of DM Intervention Participants (Required)

Throughout the first year, the delivery of the DM Intervention is consistent in all CCs. Maintenance of dietary change begins in year 2. The maintenance package consists of the following activities: group sessions, newsletters, peer-led groups and social activities.

6.12.1 Group Sessions (Required)

Maintenance of dietary change begins in year 2 and involves four required group sessions each year. The maintenance sessions provide opportunities to update nutritional information and review and practice skills for maintaining dietary change. The CCC in collaboration with the CCs, develops materials for the four required yearly maintenance group sessions. Clinical Centers are encouraged to provide suggestions or plans for maintenance phase topics. Some variation in the delivery of the DM Intervention is allowed beginning in the second year; however, the range of variation is limited. The CCs must submit any plans for DM Intervention activities to the CCC for approval at least one month prior to their implementation in the clinic.

If the number of women attending DM Intervention groups is small (fewer than eight), groups may be combined for the maintenance sessions at the CC's discretion. The CCC will develop procedures to handle combining DM Intervention groups after the first year of DM Intervention.

6.12.2 Newsletter

Beginning in the year 2, the DM Intervention participants receive a quarterly newsletter (winter, spring, summer, fall). The CCC sends copies of each newsletter to the CCs for distribution to DM Intervention participants. Participants should receive the newsletters at regularly spaced intervals throughout the year. Each newsletter includes:

- Tips on low-fat food preparation and recipes
- Behavioral topics
- Ways to enhance maintenance

The CCs are encouraged to include additional local information about restaurants, regional recipes and a question-and-answer column with responses to commonly asked questions from group participants.

6.12.3 Peer-Led Groups

During year 2 and beyond, the Group Nutritionist uses peer-led groups for DM Intervention participants who want added social support. These groups meet more frequently than quarterly under the guidance of "peer-group leaders," who are identified and trained in the local CCs. The CCs support the "peer-group leaders" by supplying resource lists of speakers, reference materials, photocopying, financial reimbursement for phone calls to study participants and mileage to the CC for supplies.

The CCC provides information to the Group Nutritionists to assist with the identification of peer-group leaders and the establishment of peer-led groups at the second Group Nutritionist training workshop. A peer-led group protocol for identification and training of local peer-led group leaders will be included in *Vol. 4 - Dietary Modification Intervention Group Nutritionist Manual, Section 2 - Group Facilitation*.

DM Intervention peer group meeting attendance is documented and key-entered using *Form 66 - DM Intervention Peer Group Meeting*. See *Vol. 3 - Forms* and *Vol. 5 - Data System, Section 8 - DM Intervention Group Data System* (to be added).

6.12.4 Social Activities for DM Intervention Participants

In addition to the planned quarterly group sessions, the CCs may have one or two annual large-group social functions (i.e., guest speakers, potlucks, food demonstrations). The purpose of these social activities is to promote social support among group members, spouses and members in other DM Intervention groups.

6.12.5 Make-Up Activities After First Year (Required)

Group Nutritionists must use the standardized make-up procedures outlined in *Section 6.10.5 – Make-Up Activities for Women Who Miss Sessions.* To determine other levels of DM participation available, refer to *Section 6.10.6 - Determining and Maintaining Levels of DM Intervention Participation (Required).*

6.13 Guidelines for Participants with Self-Reporting Scores Consistently < 15 grams/day (Optional)

The Group Nutritionist may use the following guidelines to educate DM participants who express concerns about the safety of a low fat diet or those few individuals whose self-reported fat scores are below 15 gm/day on a consistent basis. The GN may complete a dietary assessment if she/he has concerns about the adequacy or balance of a participant's eating pattern. This assessment may take up to 30 minutes to complete.

6.13.1 Identify Participants

To evaluate consistency, rather than single episodes of fat intake below 15 grams daily, the Nutritional Adequacy Working group recommends that nutritionists look at fat score trends or averages (of fat scores) over time. Suggested time frames are:

- Session 3-9 (3 sessions in a row)
- Sessions 10-18 (3 sessions in a row, or 3 months)
- Maintenance Years 2+ (2 sessions in a row, or 6 months)

The Group Nutritionist may use *Form 63* (Session Data Sheet) and/or the *Individual Progress Report* (*WHIP 0428*) to monitor and identify participants who report fat scores that are consistently less than 15 grams.

6.13.2 Contacting Participants

The Group Nutritionist may use any type of contact that will be time efficient and simplify the assessment process for both the participant and the nutritionist. An assessment may be done by phone or a visit may be arranged before or after a regularly scheduled group meeting. The assessment may take up to 30 minutes to complete.

Before talking to the participant, it is strongly recommended that the Group Nutritionist review the participant's previous self-monitoring information to identify potential discussion areas.

6.13.3 Assessing Very Low-Fat Eating Patterns

The Group Nutritionist may either use the *Outline for Group Nutritionist (Figure 6.4)* to facilitate an interactive discussion, or she/he may use the *Group Nutritionist Assessment Worksheet (Figure 6.5)* to conduct an optional interactive assessment interview.

The key areas to include when conducting an interview to assess very low fat eating patterns are listed below. Refer to *Figure 6.4 Outline for Group Nutritionist.*

- Review self-monitoring information
- Assess eating patterns
- Assess other potential areas
- Help participants identify challenges
- Clarify misunderstandings, if necessary
- Negotiate a plan to provide a better balance in eating patterns

When reviewing the self-monitoring information, the Nutritional Adequacy Working group has the following recommendations:

- Look for balance and variety in food choices. Check for a reasonable balance in saturated and unsaturated food choices. Identify participants who are consistently selecting foods that are high in saturated fats (e.g., red meats, high-fat dairy foods and desserts) while excluding foods that are sources of essential fats (polyunsaturated oils, whole grains, beans/legumes, etc.). Be aware of signs of restrained eating patterns.

- Look for other eating patterns that could influence food intake and hydration (e.g., alcohol or caffeine use, water intake, use of supplements or diuretics, etc.).

- Assess whether self-monitoring information represents typical eating pattern. For example:
  - Did the participant record only their best/lowest days?
  - Did the participant eat out more frequently than indicated on the days recorded?
- Look for potential recording errors or omissions. It is important not to assume that a fat score below 15 grams indicates a very low fat intake. Make sure the participant understands how to self-monitor and is accurate in reporting. For example:
  - Are foods left out?
  - Are portion sizes estimated correctly?
  - Are fat scores calculated correctly?
  - Are any "oil-based supplements" used, but not recorded?
- If the participant reports symptoms, (e.g., dry skin, brittle nails, etc.) check for potential misattribution. For example, rapid weight loss, environmental changes, and even inadequate water intake may contribute to dry skin.

There are two optional participant handouts available for the Group Nutritionist to use during the counseling session. The first, *Potential Ideas to Provide Better Balance in Eating Patterns* (see *E.5.14*) may be used by the Group Nutritionist and participant at the end of their discussion to identify a dietary change(s) that the participant is willing to make to improve the balance in their eating pattern. The second, *Fact Sheet-Learning about Fat* (see *E.5.15*) may be provided at the end of the discussion to help address participant questions about the safety and adequacy of the WHI low-fat eating pattern.

6.13.4 Recording Contact(s)

The Group Nutritionist should use *Form 64 (Individual Data Sheet)* to document a contact with a participant who has received optional counseling for nutritional adequacy. The "Other" category on *Form 64* should be checked off.

Figure 6.8
Outline for Group Nutritionist
Areas to Review When Assessing A Very Low-Fat Eating Pattern

I. Self-Monitoring Information
- A. Fat intake
  - 1. Average total fat grams
    - a) Weekly or monthly averages?
    - b) Comparison to fat gram goal?
- B. Self-monitoring tool used (Food Diary, Fat Scan, Keeping Track of Goals, etc.)
  - 1. Number of days?
  - 2. Food choices/selections available?
    - a) How representative of regular eating patterns?
    - b) Frequency of meals eaten away from home?
    - c) Information on frequency of use/serving size?
  - 3. Assess ability to self-monitor
    - a) Understanding
    - b) Accuracy
- C. No information about food choices or no self-monitoring information available.
  - 1. Complete a Diet History "typical day" for assessment.

II. Eating Pattern Assessment
- A. Food Groups Contributing Fat
  - 1. Assess Saturated Fat Food Sources
    - a) Protein-red meats
    - b) Dairy Foods
    - c) Grains-snacks, desserts, baked goods
    - d) Fats-butter, commercial fried foods
  - 2. Assess Unsaturated Fat Food Sources
    - a) Protein-fish, tofu
    - b) Beans and legumes
    - c) Grains-whole grains
    - d) Vegetables
    - e) Fats-nuts/seeds, peanut butter, vegetable oils (particularly Canal™, olive, safflower, sunflower or corn), mayonnaise, salad dressings
- B. Other Eating Patterns
  - 1. Restrained eating patterns.
  - 2. Water intake (average)
  - 3. Alcohol intake (average)
  - 4. Use of supplements
    - a) Probe for fat-containing supplements
    (e.g. flaxseed oil, fish oil capsules, cod liver oil, etc.)
    - b) Inform participant to include these in her fat score calculations.

III. Other Potential Areas to Assess
- A. Weight Status
  - 1. Stability of weight during last 3-6 months
  - 2. Reasons, if unstable
    - a) Weight loss program (self-imposed or commercial)
    - b) Health reasons
    - c) Major life event/stress (death in family)
    - d) Unexplained weight loss
- B. Physical Symptoms
  - 1. What are they?
  - 2. How persistent (duration of symptoms)
  - 3. Possible reasons for symptoms (other than WHI low-fat diet)
    - a) Physical (stress, age, menopause, health related problem, etc.)
    - b) Medication(s)
    - c) Environmental (changes in products, weather, etc.)

Figure 6.8 (continued)

IV. Help Participant Identify Challenges
- A. Unbalanced Food Choices
  - 1. More sources of saturated fats than unsaturated fats.
    - a) One or more food groups missing (e.g., few vegetables, no oil)
    - b) Frequently budgeting fat grams for high-fat desserts, baked goods or red meat
    - c) Over use of fat-free foods
  - 2. Lack of variety within specific food groups
    - a) Protein (red meat vs. poultry vs. fish, vs. meatless)
    - b) Vegetables (dark green leafy, yellow, etc.)
    - c) Grains (refined vs. whole grains and baked goods vs. starches)
    - d) Fats (minimal use of vegetable oils, nuts or seeds
    - e) More commercial fat-free foods (cookies, cake, crackers) vs. naturally fat-free foods (fruits, vegetables, grains)
- B. Physical or Environmental Challenges
  - 1. Physical Challenges
    - a) Difficulty chewing or swallowing.
    - b) Pain in mouth, teeth or gums.
  - 2. Environmental Challenges
    - a) Poor appetite
    - b) Medications interfere with appetite
    - c) On a special diet
    - d) Dislikes cooking
    - e) Usually eats alone
    - f) Limited finances
    - g) Fasts for periods of time

V. Identify Potential Strategies
- A. Clarify Misunderstandings
  - 1. Low-fat diet is safe, but not a zero fat diet.
  - 2. Fat-free equals calorie free and no limits
  - 3. Why you need the type of fat contributed by certain foods
- B. Negotiate Ways to Balance Eating Patterns
  - 1. Increased fat gram intake (up to goal)
  - 2. Food choices to decrease saturated food sources
  - 3. Food choices to increase unsaturated food sources (polys, monos)
  - 4. Alternating food choices made when budgeting fat – fat budgeting compromise
  - 5. Other strategies (eating alone, dislike for cooking, chewing/swallowing problems)

Figure 6.9
Group Nutritionist Assessment Worksheet
(Very Low-Fat Eating Pattern)

Note: Be sure to consider the age and ethnic background of the participant when asking about food choices and eating patterns.

NOTES

Self-Monitoring Information:

Avg. Fat Score: _____ **WHI Fat Gram Goal: _____**

Form used:_____ (diary, scan, quick scan, computer, etc.)

- Assessment based on: _____ (# of days)
- Representative of 'regular eating patterns'? ___ Yes ___ No

If 'No', why not: _____

_____

- Frequency of Meals Prepared or Eaten Away from Home:_____
(weekly average: % or average #)

Typical Day (Optional)

Morning meal/snacks:

_____
_____
_____
_____
_____
_____

Afternoon meal/snacks:

_____
_____
_____
_____
_____
_____
_____

Evening meal/snacks:

_____
_____
_____
_____
_____
_____
_____
_____

Figure 6.9 (Continued)

NOTES
Eating Pattern Assessment – Food Groups Contributing Fat
Assess balance between saturated and unsaturated food choices. Look at: 1) variety of foods eaten within each group, 2) frequency eaten, 3) average serving size. Use space below to note food choices.

Assess Saturated Fat Food Sources:

- ☐ Protein (red meats): _____
- ☐ Dairy foods: _____
- ☐ Grains (snacks, desserts, baked goods): _____
- ☐ Fats (butter, com'l. fried food): _____

Assess Unsaturated Fat Food Sources:

- ☐ Protein (fish, tofu): _____
- ☐ Beans and legumes: _____
- ☐ Whole grains: _____
- ☐ Fruits/Vegetables (olives, avocado, etc.): _____
- ☐ Fats (nuts/seeds, peanut butter, vegetable oils, salad dressings, and mayonnaise): _____

Figure 6.9 (Continued)

NOTES

Eating Pattern Assessment - Other Eating Patterns:

☐ Water use: Avg./week or day: _____ (lack = less than two 8 oz. glasses/day)

☐ Alcohol use: Avg. /week or day:_____

☐ Liquid supplements (Boost, Ensure, Slimfast, Medifast, etc.). ___ Yes ___ No

If yes, approximate amount/week or day: _____

☐ Vitamins/mineral supplements. (Probe for fat-containing supplements: fish oil capsules, flaxseed oil, etc.)

___ Yes ___ No

If Yes, specify (type and amounts): _____

_____

_____

_____

Other Potential Areas to Assess – Weight Status

❑ Stable (no change in past 3-6 months)

❑ Weight GAIN > 5 lbs. in past 3 months

❑ Weight LOSS > 5 lbs. in past 3 months

Possible reasons for weight changes:

❑ Intentional weight loss (self-imposed or program)

❑ Health-related

❑ Major life event/stress

❑ Other:_____ - (e.g., unexplained)

Comments: _____

_____

_____

Figure 6.9 (Continued)

NOTES

Other Potential Areas to Assess – Physical Symptoms of Concern

- ❑ Weight loss
- ❑ Changes in skin
- ❑ Hair loss
- ❑ Changes in fingernails
- ❑ Other:_____

- Duration of symptoms:_____(approx. length of time)

Possible Reasons for Symptoms (other than WHI low-fat diet):

- ❑ Age
- ❑ Major life event
- ❑ Stress
- ❑ Menopause
- ❑ Health-related problems
- ❑ Rapid weight loss
- ❑ Lack of water intake
- ❑ Other non-WHI diet
- ❑ Medications
- ❑ Changes in environment (weather, air conditioning, heating)
- ❑ Changes in products (detergents, cosmetics, bath products)
- ❑ Other:_____

Comments: _____

_____

Figure 6.9 (Continued)

NOTES

Help Participant Identify Challenges – Unbalanced Food Choices

More Sources of Saturated vs. Unsaturated Fats.

- ☐ One or more food group missing (e.g., few vegetables, no vegetable oils, etc.)
- ☐ Frequent budgeting of fat grams for high-fat desserts, baked goods or red meat
- ☐ Over use of fat-free commercial products (refined grains/sugar vs. whole grains; trans fats)

Lack of Variety Within Specific Food Groups:

- ☐ Protein (more red meat than poultry and/or fish; meatless meals)
- ☐ Vegetables (dark green leafy, yellow/orange, cruciferous, etc.)
- ☐ Grains (refined vs. whole grains; baked goods/sweets vs. complex carbohydrates)
- ☐ Fats (no use of vegetable oils, nuts or seeds, etc.)
- ☐ More commercial fat-free foods (cookies, cakes/pastries, crackers) vs. naturally fat-free foods (fruits, vegetables and whole grains)

Physical or Environmental Challenges:

Physical:

- ☐ Has difficulty chewing or swallowing
- ☐ Has pain in mouth, teeth, or gums
- ☐ Unable to prepare own meals/food
- ☐ Other:_____

Environmental:

- ☐ Has a poor appetite or on medications that interfere with appetite
- ☐ On a special diet
- ☐ Dislikes cooking
- ☐ Usually eats alone
- ☐ Limited finances
- ☐ Has a pattern of fasting 1 or more days each month
- ☐ Other:_____

Comments: _____

_____

_____

Figure 6.9 (Continued)

NOTES

Identify Potential Strategies

Clarify Misunderstandings (Potential areas where participant may need clarification):

- ☐ Low-fat diet is safe, but not a zero fat diet.
- ☐ Fat-free foods contain calories.
- ☐ Importance of certain types of fat

Other: _____

Negotiate Ways to Balance Eating Patterns:

Plan of Action:

_____

_____

_____

_____

_____

_____

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_____

_____

_____

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_____

Table 6.3
Summary of DM Intervention Sessions

Session Number	Session Objectives	Nutritional Topics	Behavioral Topics
	Weekly		
1	Review goals and objectives of the WHI DM Intervention. Discuss the benefits and responsibilities of being a participant. Identify the amount of fat in foods. Identify lower-fat food choices, especially fruits, vegetables and grains.	Awareness of fat in foods. Awareness of fruits, vegetables and grains.	Awareness of costs/benefits to study participants. Social support in group and home setting. Communication skills.
2	Discuss ways to reduce added fats. Use Fat Counter to calculate fat score. Use self-monitoring to evaluate dietary changes.	Awareness of current fat intake. Method to record fat intake.	Self-monitoring of dietary behavior.
3	Identify high-fat dairy foods currently used. Discuss skills for selection and use of low-fat dairy foods. Identify reasons for goal setting as a component of behavior change. Set goals using "Guidelines for Goal Setting."	High-fat dairy foods. Low-fat substitutes. Low-fat calcium sources.	Definition of problem behavior. Setting goals for behavior change.
4	Read and interpret nutrition labels and marketing techniques. Identify how other people influence their eating patterns.	Nutrition label reading. Shopping skills. Food availability.	Social influences on eating. Self-control skills.
5	Identify high-fat entrees. Discuss skills for selection and preparation of low-fat entrees. Practice modification of entree recipes. Identify strategies to accommodate friends and family in the low-fat eating plan.	Low-fat entree substitutes. Vegetarian entrees. Entree recipe modification.	Support from home eating partners. Problem solving skills. Communication skills.

Session Number	Session Objectives	Nutritional Topics	Behavioral Topics
6	Discuss skills and strategies for eating in social situations. Learn the skill of fat budgeting. List strategies for low-fat restaurant eating. Practice menu selection using local restaurant menus.	Fat budgeting skills. Low-fat dining options. Evaluation of restaurant menus.	Problem-solving skills. Communication skills.
	Every Two Weeks		
7	Learn how to use shorter self-monitoring tool (Fat Scan). Learn how to use fruits and vegetables and grains as low-fat snacks. Identify family and friends' influences on snacking patterns. Learn ways to say "no" to high-fat snacks.	Short self-monitoring tool (Fat Scan). High-risk foods. Fruit and vegetable snack alternatives.	Self-monitoring Social influences on snacking. Resistance skills.
8	Select low-fat dessert alternatives. Discuss ways sweets are used as a reward. Identify social support strategies to deal with sweets and desserts. Identify people who can help and ask for support.	High-risk food situations. Fruit dessert suggestions.	Asking for social support. Foods as reinforcers.
9	Share low-fat eating experiences with other DM Intervention participants. Identify ways eating partners can support each other.	Low-fat recipe exchange. New food preparation ideas.	Promotion of group cohesiveness.
(I)	Individual Session: Provide individual support and feedback. Discuss dietary changes made to date. Evaluate variety and balance of current eating habits. Identify potential problems and plan for long-term maintenance.	Nutritional evaluation. Current eating habits.	Evaluation of current behavior. Reinforcing change. Planning for future change.
	Monthly		
10	Review group progress. Identify potential situations that interfere with low-fat eating. Learn how to use the skill of problem solving.	Areas that interfere with low-fat eating.	Barriers to change. Self-management strategies.
11	Explain how self-talk influences actions. Identify negative thought patterns by listening to self-talk. Replace negative self-talk with positive thoughts. Identify low-fat lunch ideas.	Low-fat lunch ideas. Vegetables for lunch.	Cognitive restructuring.

Session Number	Session Objectives	Nutritional Topics	Behavioral Topics
12	Identify the challenges that vacations and holidays present to low-fat eating. Review strategies to handle vacations and holidays. Identify lower fat alternatives to modify home-baked goods.	Vacation/holiday foods Recipe modification of baked goods.	High-risk situations. Self-management strategies.
13	Discuss time-saving strategies to reduce time spent in food management activities. Plan three days of menus and make a shopping list. Identify ways to increase fish consumption.	Meal planning skills. Fish preparation ideas.	Organizational and planning strategies and skills.
14	Identify sources of complex carbohydrates. Identify and describe ways to increase complex carbohydrate intake. Discuss techniques for introducing new cuisine to family and friends.	Sources of complex carbohydrates. Tasting meatless recipes.	Communication skills. Social support.
15	Identify sources of stress that interfere with ability to change. Demonstrate strategies to cope with stress. Practice relaxation exercise. Identify methods and recipes for quick meal preparation.	Preparation of quick meals.	Stress management. Relaxation.
16	Explore the events and emotions that may trigger slips. Identify strategies to recover from a slip. Practice strategies to prevent setbacks. Taste new low-fat alternatives for "out-of-routine" situations.	High-risk foods. Low-fat alternatives for "out-of-routine" situations.	Relapse prevention.
17	Identify factors that help maintain dietary changes. Learn how loss of motivation can lead to "drift" in eating patterns. Identify self-monitoring ideas to maintain dietary changes. Learn ways to add flavor without fat.	Dietary variety. Fats and oils.	Reinforcement of current changes. Self-management. Self-help groups.
18	Review strategies that help maintain a low-fat plan. Review the progress made in WHI. Identify sources of continued support for low-fat eating.	Recipe exchange featuring new food products.	Review. Celebration. Group support.

Table 6.4
Sample DM Intervention Group Tracking Sheet

(Participants Waiting for a Group)

	Preferred Meeting Times				Dates Reached by Phone						Comments
Name of Person	**Phone Number**	**Days**	**Times (morning, afternoon, evening)**		**Date**	**Date**	**Date**	**Date**	**Date**	**Date**	**Group assignment; Reason not assigned to a group; Changes in preferred group times**
1.											
2.											
3.											
4.											
5.											
6.											
7.											
8.											
9.											

Potential codes to use for reasons not assigned to a DM Intervention group:

1 Personal illness
2 Family demands
3 Work demands
4 Out-of-town
5 Transportation
6 Other (Specify)

6.14 Targeted Message Campaign (TMC) (Required)

The Targeted Message Campaign (TMC) is an initiative to support and improve DM Intervention participation and adherence. The intent of the campaign is to help DM Dietary Change participants rediscover their motivation for participating in the WHI and to identify strategies for personal success. The campaign is founded on the motivational enhancement (ME) approach initiated with the Intensive Intervention Protocol (IIP).

The campaign materials were developed from scientific literature that supports the importance of intrinsic motivations in bringing about successful behavior change. Components of the campaign include:

- Kickoff Newsletter: Introduces the campaign and invites participants to join a fun studywide event, the Eat and Tell Challenge.
- Mailing 1 (M1): Invites participants to think about areas that are important for personal success in WHI.
- TMC Phone Call: Helps participants explore areas for personal success to identify an underlying theme.
- Mailing 2 (M2): Invites participants to consider theme-targeted activity options that support stage of readiness and motivation.

TMC activities begin in the Fall of 2000 and continue through December 31, 2001.

6.14.1 TMC Slogan, Objectives, and Themes

The TMC campaign slogan, *"It's Gotta Be You - Strength from WHIth-in,"* promotes a sense of self-reflection and internal motivation, embraces WHI cohesiveness, and supports a sense of belonging to an important group effort.

The ME approach is integrated within all TMC components to accomplish the campaign objectives as follows:
- Encourage participants to eat more fruits and vegetables while continuing to decrease dietary fat.
- Build a sense of spirit, camaraderie, and commitment to a bigger whole.
- Increase a sense of surprise, colorfulness, creativity, fun, and anticipation of possibilities.

Central to the campaign are five main themes that represent what is important for personal success in the WHI Dietary Change program. The themes are based on WHI Nutritionist input regarding common beliefs that motivate participants to commit to change and common barriers that challenge participants' ability to commit to change. The five themes are: 1) Feel the Difference, 2) Taste is Everything, 3) It's Got to Be Easy, 4) Look at Yourself, and 5) Family and Friends Count. *Figure 6.10 – Themes Overview* describes each of the campaign themes.

Figure 6.10
Themes – Overview

Color	ORANGE	GREEN	IVORY	YELLOW	BLUE
Theme (Key)	**Feel the Difference**	**Taste is Everything**	**It's Got to Be Easy**	**Look at Yourself**	**Family and Friends Count**
What's important to my personal success in WHI	To feel healthy and good about what I'm doing.	To have food taste good.	To make low-fat eating as easy as possible.	To be aware of my choices.	To give and get support from family and friends.
Focus	Feelings (physical & emotional)	Tasty choices	Easy choices	Thoughts & awareness	Family & friends

6.14.2 TMC Sample (Who is Eligible)

All DM Dietary Change participants are eligible for the TMC except those who have the following status:

a) 'Stop DM intervention and no mail follow-up' status, or
b) 'Absolutely no contact follow-up' status, or
c) Deceased.

Participants meeting the above criteria are automatically excluded from the TMC. Nutritionists may remove (or delay involvement) of eligible participants from the TMC, per their discretion based on knowledge of individual participants. Delaying participation can honor particular situations, such as illness or travel, thereby increasing the opportunity to improve DM Intervention participation and adherence. Nutritionists are encouraged to limit discretionary removal of eligible participants from the TMC because each time the decision is made to remove an eligible participant from the TMC there is a missed opportunity to improve DM Intervention participation and adherence. For additional information about modifying the TMC sample, refer *to Section 6.14.3.2 – Mailing 1 (M1) – Sent by the CCC* and the TMC WHILMA Upgrade Notes (available in the Outlook Public Folders October 2000).

6.14.3 TMC Components

The campaign includes the following sequential components: Kickoff Newsletter, Mailing 1 (M1), TMC Phone Call, and Mailing 2 (M2). Additional details about the timeline for implementing the TMC are provided in *Table 6.5* below.

Table 6.5

Components and Timeline for WHI DM Targeted Message Campaign

2000		2001									
Nov	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**
Kickoff Newsletter • Direct Mailing by CCC											
Eat & Tell Challenge Postcard returned to CCC											
		Mailing 1 (M1) ▪ Direct mailing by CCC ▪ On average, 60 mailings per CC each month									
			TMC Phone Call ▪ Telephone contact about 1 month after M1 ▪ Call conducted by CC Nutritionists (60/month) ▪ ME approach								
				Mailing 2 (M2) ▪ Mailing by CC about 1 week after call (60/month) ▪ Content based on information collected at call							

6.14.3.1 Kickoff Newsletter – Sent by CCC

The Fall/Winter 2000 issue of the Making WHIse Choices Newsletter kicks off the campaign and increases participant awareness and excitement about being a part of the WHI Dietary Change program. All Dietary Change participants receive the newsletter except those removed, per nutritionist discretion.

The newsletter invites participants to participate in a studywide event - the **Eat and Tell Challenge**. For this challenge, participants count the number of fruit and vegetable servings they ate during one day, write down the number on a pre-paid addressed postcard, and mail the postcard to the CCC. The collective goal is to consume 85,000 fruit and vegetable servings. Results of this activity are published in the Summer/Fall 2001 Making WHIse Choices Newsletter.

6.14.3.2 Mailing 1 (M1) - Sent by the CCC

Mailing 1 (M1) includes an introductory letter and a set of 20 colorful cards formatted as a table tent. The purpose of M1 is to have participants look through the cards and think about areas that are important for personal success in the WHI Dietary Change program. The cards represent the five campaign themes and set the stage for the TMC Phone Call. *Figure 6.11 – Mailing 1 – Cards by Theme* outlines which cards represent each theme.

The *TMC Tracking* screen in WHILMA provides the mechanism for Nutritionists to identify which participants receive M1 and when they begin the TMC process by receiving M1. The CCC uses the participant list from this screen to identify participants who receive M1 for a specific month. For more information about using the *TMC Tracking* screen, refer to *Section 6.14.6 – WHILMA Resources for TMC Management.*

Figure 6.11
Mailing 1 – Cards by Theme

Theme (Key)	Feel the Difference	Taste is Everything	It's Got to Be Easy	Look at Yourself	Family and Friends Count
M1 Cards	Life's Little Pleasures & You (pg. 3)	Love 'Em and Eat 'Em (pg. 5)	Easy Does It!…a WHI fable (pg. 4)	Produce Results…and see how you're doing (pg. 6)	A Chain Reaction…it starts with you (pg. 7)
	How's It Going? (pg. 12)	Jazz Up Your Salads (pg. 9)	Make It Easy (pg. 8)	Seeing is Believing (pg. 10)	Better Together (pg. 11)
	Your Recipe for Success (pg. 16)	Color Me Delicious (pg. 14)	Rumor Has It (pg. 13)	Strength in Numbers…. WHI's believe it or not (pg. 19)	The WHI Melting Pot (pg. 15)
	Only You Know for Sure (pg. 21)	Taste Magic (pg. 18)	Easy Ways to Add Fruits and Vegetables (pg. 17)	That's the Way It Is (pg. 22)	Reach Out… the art of asking (pg. 20)

6.14.3.3 TMC Phone Call - Conducted by CC staff

Approximately six weeks after M1 is sent, the Nutritionist conducts a brief phone call (15 minutes) with the participant using an ME approach. The purpose of this call is to help the participant identify and explore the theme that is important for her personal success in WHI and to lay the groundwork for Mailing 2 (M2).

Framework of the TMC Phone Call

Nutritionists use a motivational enhancement (ME) approach when conducting the TMC Phone Call. Motivational enhancement is a participant-centered approach that focuses on participants' motivations, ambivalence and ability to make choices. This approach is characterized by interpersonal style as well as use of particular skills.

Key elements of a ME interpersonal style include:

1. **Understanding**
   - Empathetic and careful listening in a non-judgmental, warm and supportive manner.
   - Seeing things from the participant's perspective and respecting whatever decision she makes about health behavior change.
2. **Participant-Centered**
   - Encouraging the participant to be active in making decisions about her behavior change.
   - Eliciting motivation for change from the participant.
3. **Collaborative**
   - Working together to determine the best course of action for change.
   - Sharing of ideas, goals and responsibility.
4. **Individualized**
   - Tailoring intervention approaches to match the participant's needs and readiness to change.
   - Moving at the participant's pace.
5. **Emphasizing Freedom of Choice**
   - Acknowledging that the decision if, when, and how to change is the participant's.
   - Avoiding "restrictive" messages (e.g., "you have to," "you must," "you can't").

Key skills used within a ME approach include:

- Asking open-ended questions.
- Reflective listening.
- Summarizing.
- Creating discrepancies to encourage further exploration on the part of the participant regarding her chosen theme.

Purpose of the TMC Phone Call is to:

1. Help the participant identify which of the five themes, introduced in Mailing 1 (M1), is most important to her participation/success in WHI.
2. Explore the reasons why the participant chose the theme.
3. Set the stage for Mailing 2 (M2).

Combining these elements of interpersonal style and particular skills allows the Nutritionist to achieve the call purpose. The Nutritionist establishes rapport with the participant, assists her in choosing a theme, explores and summarizes why she chose the theme, and peaks her interest in M2.

A major focus of the call involves exploring the participant's theme of choice. The goal is for the participant to look at how her theme of choice can help her become more successful in WHI. This exploration helps her build on what she identifies as important. This exploration also peaks her interest in M2, since the materials are theme-targeted.

Figure 6.12 - TMC Phone Call Overview provides a general structure to guide the Nutritionist through the TMC Phone Call. *Figure 6.13 - TMC Phone Call Guide* provides sample questions and strategies to assist the Nutritionist in achieving the purpose of the call using a ME approach. Suggestions to assist Nutritionists in getting conversations back on track and more focused following a period of drift from the purpose of the call are provided in *Figure 6.14 - Getting Back on Track*.

The general theoretical background, goals, and key elements of motivational enhancement (ME) are provided in *Vol. 2, Appendix G.5 – Motivational Enhancement Training August 1999. WHI Intensive Intervention Protocol.*

Figure 6.12
TMC Phone Call Overview

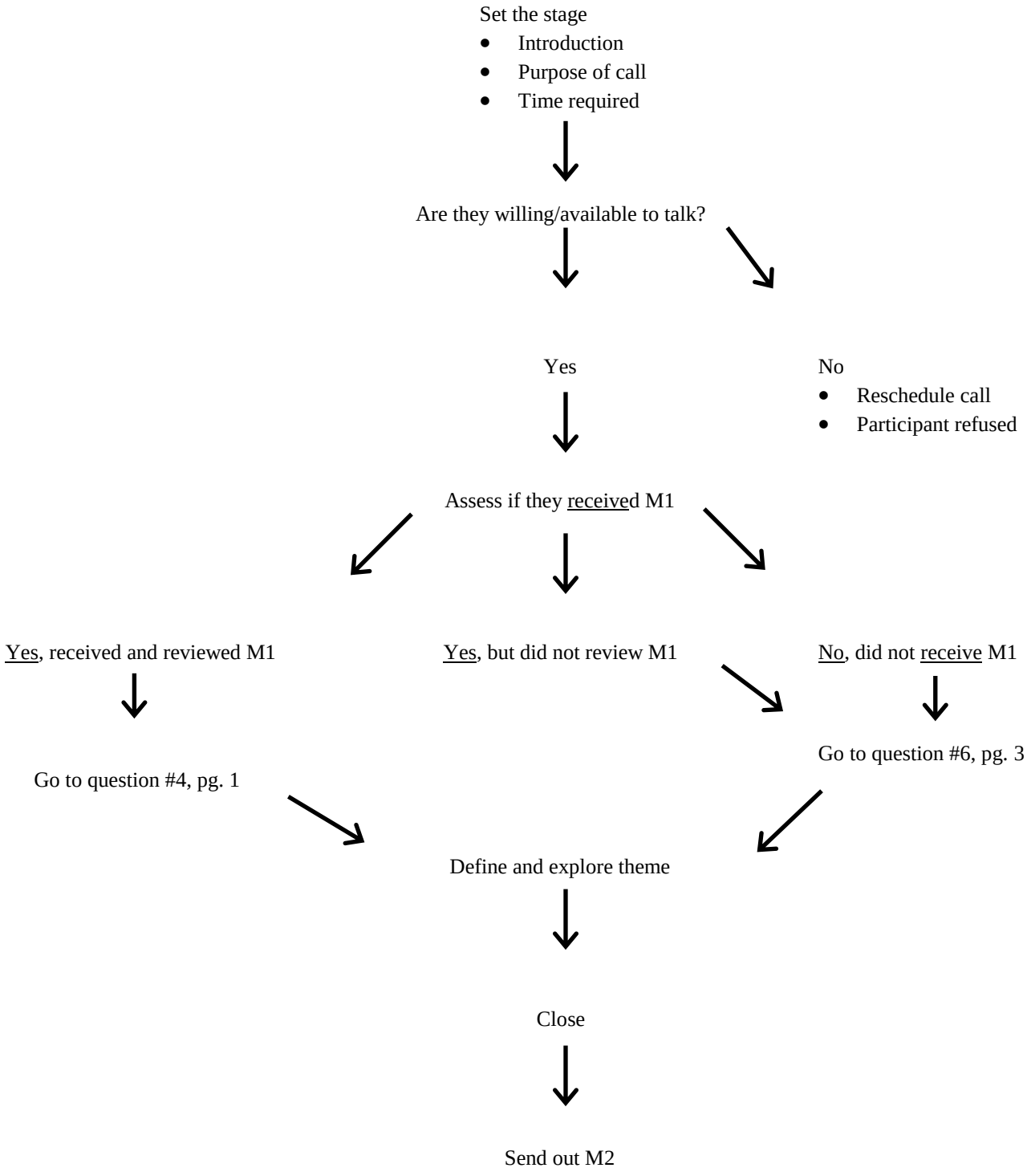


Figure 6.13
TMC Phone Call Guide

Purpose:

1. Help the participant identify which of the five themes, introduced in Mailing 1 (M1), is most important to her participation/success in WHI.
2. Explore reasons why participant chose the theme.
3. Set the stage for Mailing 2.

1. Introduction: Introduce yourself, describe the purpose of the call, share the expected time for the call, establish if this is a good time to talk, and ask permission.	**EXAMPLE:** *"Hello This is _____ from WHI……., may I please speak to _____? I'd like to take a few minutes of your time to check in with you and follow up on the "It's Gotta be You" packet of cards we recently sent you. This packet contains a variety of colorful cards. The cards reflect a variety of things that a woman may find important when making dietary changes. It came in a medium envelope with a picture of a woman on the outside. What I would like to do is talk with you for about 15 minutes about your reactions to these cards and which ones YOU identify as important when making dietary changes. Is now a good time for you to talk?"*
• If **YES:** go to #2. • If **NO:** Set up an appointment: date/time.	**EXAMPLE:** *"When would be a better time for me to call you back?"*
2. Assess whether the participant <u>received</u> the cards. • If **YES:** go to #3. • If **NO**: **Go to #6**.	**EXAMPLE:** *"Do you recall <u>receiving</u> these cards that I just described?"*
3. Suggest having the cards available to discuss during the call and assess whether the participant <u>reviewed</u> the cards before the call. • If **YES**: go to #4. • If **NO** (Not handy or did not review): **Go to #6**.	**EXAMPLE** *"Do you have the cards handy or near by? The reason I ask is that it will be helpful to have them on hand as we talk about them. I can hold on the phone while you get them."* *"Have you had the opportunity to review the cards?"*
4. Discuss the participant's thoughts about the cards: Use open-ended questions to start the conversation. Remember to reflect and summarize.	***EXAMPLE:*** *"I'd like to spend a few moments hearing from you what you think about the cards. Is that okay with you?"* ***Use An Open-Ended Question:*** • What were your reactions to the cards? • What did you like about the cards? • What, if anything, did you find useful about the cards? • What did you learn from the cards? • What would you like to share about the cards?

REMEMBER TO REFLECT! TELL HER WHAT YOU HEARD HER SAY.

Figure 6.13 (cont.)

5. Help the participant identify which theme is most important to her success in WHI. Have an open discussion, reflecting as you go!

EXAMPLE: *"As you may have noticed, there are several colored cards in the booklet.*

I'm curious…."

Use An Open-Ended Question:

- Which theme did you choose?
- Which one(s) did/do you find yourself most drawn to?
- Which card color did you like the most?
- Look on page 23. Which of the themes stands out for you?

- If the participant easily identifies a theme, go to #7.
- If participant struggles with choosing a theme, **Go to #6.**

6. If participant needs help in choosing a theme (suggested approaches):

Participant did not receive the cards OR did not review the cards.

EXAMPLE:

"Even if you did not receive the cards… ***[OR]***
"Even if you did not get the chance to review the cards…

… it would great if I could talk with you a bit. This should take about 15 minutes. Is now a good time for you to talk?"
[If NO - Reschedule].

"*Great. What I am going to do is read some phrases to you one at a time. After I read each phrase, I want you to tell me if it is important to you when making dietary changes. Would this be okay with you?"*
"Great. I will read a phrase and then you'll tell me either 'yes', that is important for me when making dietary changes, or 'no', that is not important for me when making dietary changes. There are no right or wrong answers. Any questions before we begin?"

USE THE PHRASES LISTED UNDER THE 'WHAT IS IMPORTANT TO MY SUCCESS' SECTION FOR EACH THEME ON PAGE 23 OF THE CARDS.

Participant is having a hard time choosing a theme.
EXAMPLE:

"That's okay if you're not sure which one to choose. Let's try this…I am going to read each phrase one at a time and you tell me how you would rank them on a scale from one to five. One being not very important when making dietary changes, and five being extremely important when making dietary changes. There are no right or wrong answers. Any questions before we begin?"

TIPS:

If participant has M1 in front of her:

"You may find it helpful if we read the phrases on page 23 of the cards together. The phrases are listed under the word, "Key" about ¾ of the way down the page. Let me know when you're ready."

If participant does not have M1 in front of her:

"It may be helpful if you write the phrases down on paper. This way you can see them in front of you. I will read them to you one at a time. Ready…"

USE THE PHRASES LISTED UNDER THE KEY FOR EACH THEME ON PAGE 23 OF THE CARDS.

Participant chooses more than one theme.

EXAMPLE:

"You named three themes that you see as equally important to you when making dietary changes. Now what I would like you to do is put them in order from one to three. One being the most important to you and three, although still important, may not stand out as much as the other two. Although this may be a hard choice, I know you can do it! Remember—there are no right or wrong answers. This is your choice. I will read them again…."

ONCE PARTICIPANT HAS CHOSEN A THEME, GO TO #7

Figure 6.13 (cont.)

7. Summarize.

EXAMPLE: *"Based on what you have just shared with me, it sounds like _____is/are important to you and appeals to you the most when making dietary changes. I want to emphasize that this does not mean that the other themes are not important, just that this one theme stands out more than the others. What else would you like to add?"*

8. Explore reasons for choosing theme, using open-ended questions and reflections.

EXAMPLES FOR EACH THEME BELOW:

Remember to reflect after each question then summarize at the end.

Feel the Difference:

1. *Tell me a bit about why it's important for you to feel healthy and good about what you're doing when making dietary changes. What else…?*
2. *If you could feel healthier and better about what you're doing when making dietary changes, what would need to happen?*
3. *If you decide to, how might you make this happen*?

Taste is Everything:

1. *Tell me a bit about why it's important for your food to taste good when making dietary changes. What else…?*
2. *If your food could taste better when making dietary changes, what would need to happen?*
3. *If you decide to, how might you make this happen?*

It's Got to be Easy:

1. *Tell me a bit about why it needs to be easy to eat low fat when making dietary changes. What else…?*
2. *If low-fat eating could be easier, what would need to happen when making dietary changes?*
3. *If you decide to, how might you make this happen?*

Look at Yourself:

1. *Tell me a bit about why it's important for you to be aware of your choices when making dietary changes. What else…?*
2. *If you could be more aware of your choices when making dietary changes what would need to happen?*
3. *If you decide to, how might you make this happen?*

Family & Friends Count:

1. *Tell me a bit about why it's important for your family and friends to be involved when making dietary changes. What else…?*
2. *If your family and friends could be more involved when making dietary changes, what would need to happen?*
3. *If you decide to, how might you make this happen?*

REMEMBER: WHEN EXPLORING THE THEME—AVOID GIVING ADVICE UNLESS SHE ASKS FOR IT.

9. Close the conversation and introduce Mailing 2.

EXAMPLE: "*We are done! Be sure to watch your mailbox because in the coming weeks you will receive a folder with more ideas and activities around the theme that you said was most important to you. We really hope that you will enjoy them*! *We also included some great recipes."*

10. Express your appreciation and gratitude for her participation.

EXAMPLE: *"Mrs. _____, I really want to thank you for taking the time to talk with me today. Your participation in WHI is a valuable contribution to women's health. We greatly appreciate your time, energy and efforts!"*

Figure 6.14
Getting Back on Track

Getting Back on Track: Keeping the Conversation Focused

One of the greatest challenges in a "brief" telephone call is actually keeping it brief. Yet, we feel uncomfortable interrupting participants, especially when we want them to come back! Yet, it is important to try to keep the phone conversations brief, if possible. Below is a skill that may help you in keeping conversations brief, respectful and useful.

Summarize and Shift!

Summarizing is basically mirroring or reflecting back to the participant what you heard them say. The difference between summarizing and reflecting is that the former pulls together all of the pieces of a conversation. In other words, it is a "big reflection."

Shifting is a way to move the conversation in another direction. This is useful when you encounter resistance, or the participant is wanting to talk about other things and you are feeling crunched for time.

Below is an example of how you can "summarize and shift:"

Mrs. Smith: *"Of course taste is important to me! I won't eat it if it doesn't taste good. Would you? Some of the food I've had lately has been good and some has been so bad. Just the other day, I had lunch with my friend, Joan. She thinks she is a great cook, but she's not as good as she thinks! She lives over in Rochester. I have to take two buses to get there! Anyway…she cooked this chicken that was so dry that it was like chicken jerky! It hurt to chew it. That reminds me, I have to take the chicken out of the freezer or I won't be able to have it for dinner tonight. I found a great new recipe. Her chicken was not only dry; it also didn't have any flavor. Maybe she should add some of that seasoning stuff—Mrs. Dash? That may help……"*

Nutritionist:
"Mrs. Smith, let me jump in because I want to make sure that I am hearing you correctly. What you are saying is that your food must taste good, and that sometimes adding some seasonings can really help a dish."

"I need to stop you so I can make sure that I've heard you right. I want to make sure that I get what's important to you! You say that if your food isn't flavorful, you are not going to be happy. It must have some amount of flavor for it to be worth eating."

- After you summarize, shift direction by asking an open-ended question:
- Shifting direction allows you to move the participant from the previous conversation onto a new topic.

Nutritionist:	"*What other themes did you see as important?"*
('No' scenario)	*"Now I am going to read you another statement and you tell me if it is important to you or catches your attention: It's Got to Be Easy—low-fat eating must be as easy as possible."*

- Remember to always end a conversation with a summary of what you discussed.
- Every participant is different. It may be very important to allow time for "chit-chat" prior to attending to the purpose of the call.

Good luck!

6.14.3.4 Mailing 2 (M2) - Sent by the CC

Mailing 2 (M2) is a folder that contains: a) one theme-targeted activity packet, b) four regional menus with recipes and a shopping list, and c) a seeded flower paper. The purpose of M2 is to provide a theme-targeted menu of options that allows the participant to choose an action or activity consistent with her stage of readiness and motivation.

There are six different activity packets, one for each of the five themes and a general packet. The general packet (*It's Gotta Be You*) consists of a combination of activities from the various themes. Nutritionists use the general packet in the following situations:

- When the TMC Phone Call is not done because the participant was: a) not appropriate for the TMC call, b) could not be reached for the TMC call, or c) declined the TMC call.
- When the participant is unable to identify a theme during the TMC Phone Call.

Each M2 activity packet includes six options (two targeted to participants who are "not ready", two targeted to participants who are "unsure", and two targeted to participants who are "ready to change"). Participants receive activities for all three stages of readiness to acknowledge that stage of change is fluid. The "not ready" activities invite women to think more about what is important to them in WHI. The "unsure" activities prompt exploration of ambivalence about dietary change. The "ready" activities invite women to consider action to stimulate or maintain dietary change. *Figure 6.15 – Mailing 2 Activities by Readiness & Theme* provides an overview of each activity, including stage of readiness, general description, and theme-targeted content.

The Nutritionist sends M2 (including the appropriate theme-targeted activity packet) to the participant as soon as possible after the TMC Phone Call contact (ideally within one week). Participants receive only one theme-targeted activity packet.

<u>Assembling Mailing 2:</u>

The CC is responsible for assembling the contents of M2 as follows:

1. Insert the following pieces into each folder:
    - 1 seeded flower paper in the slot provided in the bottom left section of the folder.
    - 4 regional recipe cards in the right section of the folder.
    - 1 theme-targeted activity packet in the center section of the folder.
2. Place/affix a TMC logo sticker (CCC provided) on the front of each envelope (CC provided).

Careful planning was used to design theme-targeted materials that provide equal emphasis on the three different readiness to change levels. For this reason, nutritionists are strongly encouraged not to include additional materials in the M2 folder.

Figure 6.15
Mailing 2 Activities by Readiness & Theme

Readiness	Activity	General Description	Theme – Targeted Content	
Not Ready	What It Means to Me	An activity to help the participant think about what her identified theme means to her.	Feel the Difference	What does feeling healthy and good mean to you?
			Taste is Everything	What does having great tasting food mean to you?
			It's Got to Be Easy	What does having quick and easy low-fat choices mean to you?
			Look at Yourself	What does tracking progress and being aware of choices in WHI mean to you?
			Family & Friends Count	What does involving your family and friends in WHI mean to you?
	One Day at a Time	An activity to help the participant think about how easy or hard it was on a given day to focus on WHI.	Feel the Difference	The positive impact that WHI has on your life may be more obvious on some days than others—your energy level, how you feel physically, your sense of accomplishment and much more. Think about today. How did your WHI activities feel? [Not Great – Great!]
			Taste is Everything	On some days, you may feel more satisfied with your food than on other days. Think about today. How would you say your food tasted overall? [Bland & Boring – Absolutely Delicious]
			It's Got to Be Easy	Some days may go more smoothly than others. Think about today. How easy or difficult has it been to keep WHI on your mind? [Difficult – Easy}
			Look at Yourself	You may be more conscious of your WHI choices on some days than on others. Think about today. How aware were you of your WHI choices? [Not Aware – Very Aware]
			Family & Friends Count	The positive impact that your family, friends, co-workers, and neighbors have in supporting your WHI efforts may be more obvious on some days than on others. Think about today. Did you have the support you needed? [Felt Unsupported – Felt Supported!]

Figure 6.15 (Cont.)

Readiness	Activity	General Description	Theme – Targeted Content	
Unsure	I Can Choose	An activity to help the participant think about her interest/motivation to take action that supports meeting WHI goals.	**Feel the Difference**	Activities about feeling good (physically and emotionally) about WHI participation: • List the ways WHI helps you feel healthy. • Eat a fruit or vegetable that makes your body feel good. • Identify the thing that makes you feel most happy about being a part of WHI. • Pat yourself on the back for all you do for WHI. • My idea:
			Taste is Everything	Activities about taste: • Eat a favorite fruit or vegetable. • Explore new seasonings: spices, herbs or flavored vinegar. • Look for new recipes. • Call a group member who likes to cook and ask her for ideas. • My idea:
			It's Got to Be Easy	Activities that are easy: • Grab a fruit or vegetable for a snack. • Eat 2 vegetables for dinner. • Make a salad into a meal. • Drink your fruit - mix up a smoothie. • My idea:
			Look at Yourself	Activities about being aware of choices: • Fat budget before you eat a high-fat meal away from home. • Think about your food choices on the days you don't record. • Practice positive self-talk. • List the things you do routinely to eat low fat. • My idea:
			Family & Friends Count	Activities about the importance of family and friends: • Ask for help with your biggest WHI challenge. • Share a low-fat meal with a friend or family member. • Talk with your family or friends about what being in WHI means to you. • Attend more WHI group meetings. • My idea:

Figure 6.15 (Cont.)

Readiness	Activity	General Description	Theme – Targeted Content	
Unsure	Now & Then	An activity to help the participant identify and explore the importance (past and present) of a theme-targeted subject.	Feel the Difference	What are a few of your eating habits from the past? What new habits have you discovered since joining WHI? What about your new eating habits makes you feel good?
			Taste is Everything	What are a few of your favorite foods from the past? What delicious new foods have you discovered by participating in WHI? What makes your new favorites important to you?
			It's Got to Be Easy	What are a few of your favorite foods from the past that are easy to prepare and eat? What are the new easy food favorites you've discovered by participating in WHI? What makes your new favorites important to you?
			Look at Yourself	What are a few of your eating habits from the past? What new habits have you discovered since joining WHI? What differences do you see in your eating habits since joining WHI? What makes your new eating habits important to you?
			Family & Friends Count	What are some of the most important ways you helped your family and friends in the past? How has your participation in WHI helped your family and friends? What makes helping your family and friends important to you?

Figure 6.15 (Cont.)

Readiness	Activity	General Description	Theme – Targeted Content	
Ready	Secrets to My Success	An activity to help the participant assess eating behaviors for the purpose of identifying an action step that supports meeting WHI goals.	Feel the Difference	How do your servings compare to others in WHI? What ideas do you have for ways to boost fruits and vegetables or cut fat that would help you feel healthy and good? Choose one you might do and write it here: _____.
			Taste is Everything	How do your servings compare to others in WHI? What ideas do you have for ways to boost fruits and vegetables or cut fat that would be tasty and delicious? Choose one you might do and write it here: _____.
			It's Got to Be Easy	How do your servings compare to others in WHI? What ideas do you have for ways to boost fruits and vegetables or cut fat that would be easy to do? Choose one you might do and write it here: _____.
			Look at Yourself	How do your servings compare to others in WHI? What ideas do you have for ways to boost fruits and vegetables or cut fat? Choose one you might do and write it here: _____.
			Family & Friends Count	How do your servings compare to others in WHI? What ideas do you have for ways to boost fruits and vegetables or cut fat that would be popular with family or friends? Choose one you might do and write it here: _____.

Figure 6.15 (Cont.)

Readiness	Activity	General Description	Theme – Targeted Content	
Ready	Seeds of Change	An activity to help the participant identify an action step that supports meeting WHI goals.	Feel the Difference	Goals about <u>feeling good</u> (physically or emotionally) about WHI participation: • Take time in the next month to think about all the dietary changes you've made since joining WHI. • Eat a low-fat food today that makes you feel healthy. • List the positive feelings you had about the WHIse choices you made this week. • At the end of each day, think about the ways WHI helps you feel healthy - - do this every day for a week.
			Taste is Everything	Goals about <u>taste</u>: • Try one new low-fat meal each week for a month. • Combine different vegetables and fruits for new flavors and colors - - do this for 3 days this week. • Browse through low fat cookbooks and WHI recipes to find 4 new recipes to try in the next month. • Experiment with a new low-fat seasoning during the next week.
			It's Got to Be Easy	Goals about doing something <u>easy</u>: • Have a fruit or vegetable with every evening meal for a week. • Keep a daily tally of your fruit & vegetable servings for a week. • Look through your WHI recipe collection during the next month to find recipes that are easy. • Eat a meatless meal once a week for a month.
			Look at Yourself	Goals about <u>being aware</u> of choices: • Consider tackling a WHI challenge you've been thinking about. • Keep track of your fruits and vegetables every day for a week. • Count fat grams every time you eat away from home in the next month. • The next time you choose a high-fat food, take a few moments to think about the reasons you're eating it.
			Family & Friends Count	Goals about the <u>importance of family and friends</u>: • Talk with the people who support you in WHI - - tell them what they currently do that helps you. • Prepare a meal for a friend - - ask her to pick the low-fat entrée. • Attend an additional WHI group meeting each year. • Exchange low-fat recipe ideas with family members or friends.

6.14.4 TMC Data Collection

The Nutritionist uses *Form 67 – TMC Phone Call (Ver. 1)* and progress notes to document the result of the participant's TMC Phone Call contact.

Form 67

Form 67 – TMC Phone Call (Ver. 1) is a data collection form that documents the following information:

- If the participant received the TMC Phone Call, including reasons for not receiving the call. And, if the participant did not receive the call, whether the Nutritionist opted to send the *It's Gotta Be You* M2 packet.
- If the participant received and reviewed M1 before receiving the TMC Phone Call.
- Theme the participant identified during the TMC Phone Call.
- If the participant was unable to identify a theme during the TMC Phone Call (and, therefore, received the *It's Gotta Be You* M2 packet).
- If the participant refused M2.
- Date M2 packet was sent (optional).

Form 67 – TMC Phone Call is computer-generated from WHILMA. Refer to the WHILMA v. 43 Upgrade Notes (available in the Outlook Public Folders in January 2001) for information about how to generate this form from WHILMA.

For each participant scheduled to receive the TMC Phone Call, the form shows the following pre-printed information:

- Participant name and ID (including barcode).
- Participant phone number (including work number if specified OK to call).
- Participant DM Intervention status (active vs. stopped).
- Nutritionist ID.
- Group number.
- Participant Mailing 1 Month.
- Participant TMC Call Month.
- TMC Notes (key-entered in the TMC Tracking Screen).

The Nutritionist generates *Form 67 – TMC Phone Call* before contacting the participant for the TMC Phone Call, most likely the month prior to the call. Example: in January, the Nutritionist generates the form for all participants scheduled to receive the TMC Phone Call in February. The form (pre-printed with the participant-specific information outlined above) can then be used as a 'tickler' file for managing upcoming calls. Refer to the WHILMA v. 43 Upgrade Notes for information about parameters that allow the Nutritionist to generate the form using various selection criteria (e.g., TMC Phone Call Month, Nutritionist ID, Group #, etc.). The programming for generating this form also includes the capability to print participant mailing labels for M2. This allows the Nutritionist to generate *Form 67 – TMC Phone Call* and the corresponding M2 mailing label at the same time. Refer to the WHILMA v. 43 Upgrade Notes for information about printing the M2 mailing labels.

The Nutritionist completes and key-enters *Form 67 – TMC Phone Call* only when: a) the TMC Phone Call has been done or b) the Nutritionist makes the final determination that the TMC Phone Call will not be done.

Below are examples of how to complete *Form 67, Qx. 3 – Contact Result* in various situations. For complete details and instructions, refer to *Vol. 3 – Forms, Instructions for Form 67 – TMC Phone Call (Ver. 1)*

- *Participant Not Appropriate for TMC Call* (Qx. 3 – Option 1): The Nutritionist marks this option when her/his clinical judgement indicates that the participant should not be approached for the TMC Phone Call. This decision may occur because a participant has a crisis situation (e.g., serious personal or family illness, the death of spouse, etc.). As noted above, the Nutritionist completes and key-enters the form for this situation only when the final determination is that the TMC Phone Call will not be done. At this point, the Nutritionist has the option to send the *It's Gotta Be You* M2 packet to a participant who will not receive the TMC Phone Call.

- *Participant Not Reached for TMC Call* (Qx. 3 – Option 2): The Nutritionist marks this option when her/his judgement indicates that the participant cannot be reached for the TMC Phone Call. As noted above, the Nutritionist completes and key-enters the form for this situation only when the final determination is that the TMC Phone Call will not be done. Clinical Center discretion determines the minimum number of attempts to make before deciding that the participant cannot be reached. Suggestion: attempt to contact the participant 10 times (different days/times) before making the final determination that she cannot be reached for the TMC Phone Call. At this point, the Nutritionist has the option to send the *It's Gotta Be You* M2 packet to a participant who will not receive the TMC Phone Call.
- *Participant Declined TMC Call* (Qx. 3 – Option 3): The Nutritionist marks this option when the participant is reached, but declines the TMC discussion (i.e., participant indicates that this is not a good time and is unwilling to re-schedule the call). As noted above, the Nutritionist completes and key-enters the form only when the final determination is that the TMC Phone Call will not be done. At this point, the Nutritionist has the option to send the *It's Gotta Be You* M2 packet to a participant who will not receive the TMC Phone Call.
- *TMC Call Done* (Qx. 3 – Option 4): The Nutritionist marks this option when the TMC Phone Call (using a ME-style) discussion has occurred and Form 67, Qxs. 3.2 – 3.5 have been answered.

Progress Notes

In addition to *Form 67 – TMC Phone Call* (Ver. 1), the Nutritionist will want to keep notes about each TMC Phone Call. The purpose of the progress notes is to help the Nutritionist manage TMC Phone Call contact information that is not data entered, but is important for continuing to support and build the participant's motivation in future contacts. The notes include, but are not limited to, information gathered during the exploration of the participant's identified theme. Notes about exploration of the identified theme might include the participant's:

- Description of what her chosen theme means to her.
- Description of why that particular theme is important to her.
- Ideas about how things surrounding her identified theme could be different in order to enhance her personal success in WHI.
- Thoughts about how she might make these differences happen.

Refer to *Figure 6.13 – TMC Phone Call Guide* for examples of ways to explore the participant's identified theme. Keeping notes is required; the method used to keep the notes is the Nutritionist's option.

6.14.5 TMC Management

TMC activities begin in the Fall of 2000 with the WHI Making WHIse Choices (Kickoff) newsletter and continue through December 31, 2001.

The Lead Nutritionist appropriately allocates resources to complete TMC activities per the studywide timeline. To manage the TMC workload, the Lead Nutritionist does the following:

- Identifies which participants will participate in the TMC.
- Identifies when participants will begin the TMC process by receiving M1.
- Determines the number of participants each month that will begin the TMC process by receiving M1.
- Determines the number of participants who will receive the TMC Phone Call contacts each month.
- Defines the process for assembling and mailing M2 each week.
- Tracks participant progress through the TMC.

When allocating staff resources for the TMC, the Lead Nutritionist also considers the following:

- The number of nutrition staff available to conduct the TMC Phone Call contacts (e.g. workload distribution, part-time staff, vacations, etc.).
- Availability of participants for the TMC Phone Call contacts (e.g. available only on evenings or weekends, or extended travel (snowbirds).
- CC staff resources available to assemble and mail the M2 packets to participants.

The Lead Nutritionist manages local TMC operations using WHILMA resources as outlined in *Section 6.14.6 – WHILMA Resources for TMC Management.*

6.14.6 WHILMA Resources for TMC Management

The *TMC Tracking* screen, *Mailing 1 Summary* screen (and corresponding *Mailing 1 Summary* report), and the *TMC Member Tracking* report provide tools to help the Lead Nutritionist schedule and monitor progress of TMC activities. Refer to the TMC WHILMA Upgrade Notes (available in the Outlook Public Folders in October 2000) and the WHILMA v. 43 Upgrade Notes (available in the Outlook Public Folders in January 2001) for details about using the WHILMA resources.

TMC Tracking Screen

The TMC Tracking screen provides the mechanism for the Lead Nutritionist to determine:

- Which participants will participate in the TMC.
- When each participant will begin the TMC process by receiving Mailing 1.
- Each participant's TMC language preference.

The *TMC Tracking* screen (published to CCs October 2000) distributes participants evenly by M1 month (January through August 2001), Nutritionist, and DM group. Clinical Centers may modify this distribution as necessary (within the January through August timeframe) to meet local participant and staffing needs. However, changes to the *TMC Tracking* screen must be final before the scheduled database freeze as outlined below.

CCC Database Freeze. The CCC freezes the *TMC Tracking* screen data for M1 approximately 6 weeks before each M1 Month begins. For example, the CCC will freeze the *TMC Tracking* screen for the March mailing on January 15th. Nutritionists finalize the participant list for each M1 Month **the day before** the scheduled database freeze. Refer to the TMC WHILMA Upgrade Notes for the exact date for each mailing month.

Mailing 1 Summary Screen

The *Mailing 1 Summary* screen provides a summary of the distribution of participants by M1 month and by Nutritionist. It provides a summary of each Nutritionist's potential TMC workload for the eight-month period between January and August 2001. Nutritionists can use this summary screen to obtain a quick picture of their workload for TMC Phone Call contacts. For example, M1s mailed in January will result in TMC Phone Calls in February. Any changes made in the *TMC Tracking screen* will be reflected in the *Mailing 1 Summary* screen. A hardcopy of the *Mailing 1 Summary* screen may be obtained by a) printing the screen (click on the Print Screen button) or b) running and printing the *TMC Mailing 1 Summary* (TMC002) report.

TMC Member Tracking Report

The *TMC Member Tracking* (TMC001) report includes all DM Intervention participants eligible for TMC and provides information about several key TMC variables (i.e., Participant Name and ID; DMI Status; Nutritionist ID; DM Group; M1 Month; TMC Call Month; TMC Status; TMC Phone Call Contact Date; TMC Phone Call Contact Result; Theme; Date M2 Mailed).

The Lead Nutritionist (or designee) uses the *TMC Member Tracking* report to manage local implementation of the TMC. The report facilitates the following:

- Identifying the M1 and TMC Phone Call month for each participant.
- Tracking TMC Phone Call date and result for each participant.
- Tracking the theme chosen by each participant.
- Tracking the M2 mailing date (optional) for each participant.

It is recommended that Nutritionists run the *TMC Member Tracking* report monthly. For more details about running the *TMC Member Tracking* report, refer to the WHILMA v. 43 Upgrade Notes (available in the Outlook Public Folders in January 2001).

6.14.7 TMC Integration with Maintenance Sessions

The quarterly DM Maintenance sessions present an opportunity to provide follow-up for M2. After the participants in a given DM group have received M2, the Nutritionist is encouraged to use the *Group Sharing/Next Steps Follow-up* segment at the beginning of the next session to engage participants in a discussion about the theme-targeted activity packets. The purpose of the group discussion may be any, or all, of the following:

- Share experiences using the theme-targeted activity packets.
- Share discoveries related to a specific activity (e.g., *What It Means to Me*, etc.).
- Discuss and explore specific activities that pertain to the whole group (e.g., *Secrets to My Success*, etc.).
- Help participants continue to explore ambivalence, choices, and confidence in considering dietary changes around their specific targeted themes.

The discussion questions could be general (e.g., "What activities have you tried?") or focused on a specific activity (e.g., Would someone like to share your response to the *I Can Choose Activity*?).

6.14.8 TMC Evaluation

The FFQ will be used to evaluate the TMC. The TMC evaluation has the following objectives:

- Monitor completeness of the protocol implementation at the clinic level.
- Estimate effect of the TMC on change in percent energy from fat in Dietary Change participants.

Evaluation of Protocol Completeness

The CCC will use data collected from *Form 67 – TMC Phone Call* to evaluate TMC implementation. These contacts will provide the numerator for determining the completeness of the protocol implementation, where the denominator is the (live) Dietary Change cohort. This procedural monitoring will provide an unbiased assessment of the degree of protocol implementation, both trialwide and at the clinic level.

Estimate Effect of the TMC on Change in Percent Energy from Fat in Dietary Change Participants

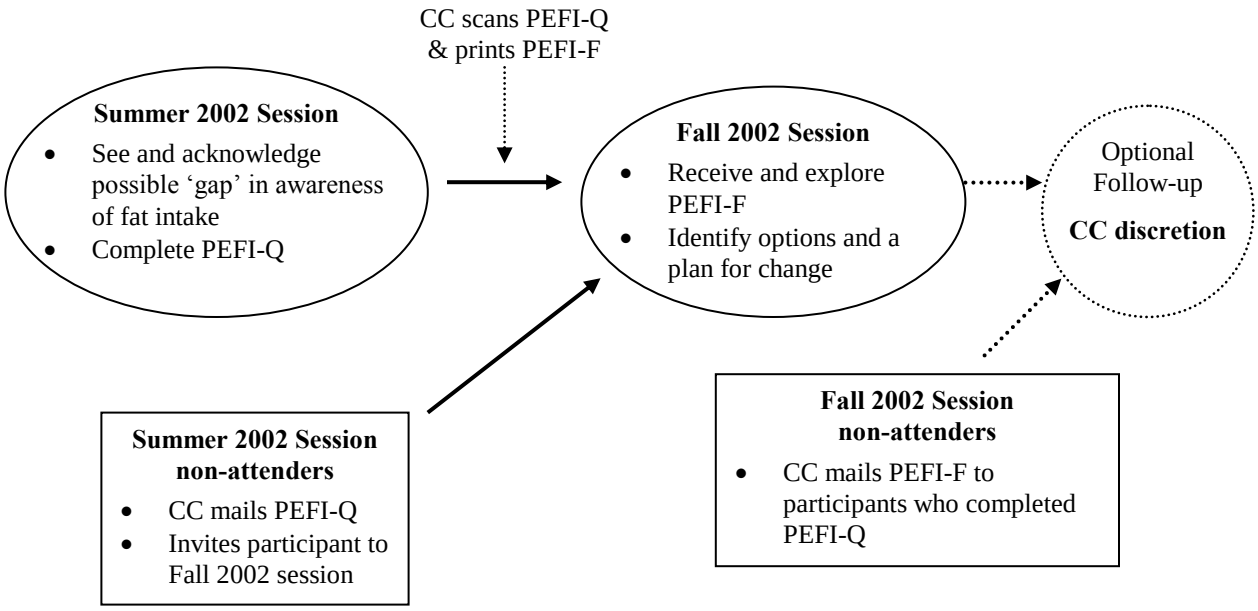
The CCC will conduct a before-and-after analysis based on the fact that 100% of Dietary Change participants complete an AV-1 FFQ and about a third will complete an FFQ during 2001, while the TMC is being implemented. Therefore, we will be able to compare participants who completed an FFQ before receiving the TMC (i.e., a TMC control group) with participants who completed an FFQ after receiving the TMC (i.e., a TMC intervention group). The outcome variable will be change in percent energy from fat from AV-1 to the most recent FFQ and the model will be controlled for potential covariates such as age, race/ethnicity, education, visit year, and clinic effects. These data permit a pairwise analysis of the effect of the TMC on Dietary Change participants' fat intake in the "TMC control" vs. "TMC intervention" groups. The sample sizes should provide a reliable trialwide estimate but are likely too small to provide precise clinic-specific estimates of the TMC effect.

We acknowledge that the TMC protocol, as implemented in WHI, is not designed for a rigorous test of the effectiveness of this intervention campaign component in reducing fat intake for, at minimum, the following reasons: variability in administration; concurrent effects of the main intervention; and, lack of an appropriate comparison group.

6.15 Personalized Evaluation of Fat Intake (PEFI)

The Personalized Evaluation of Fat Intake (PEFI) is an augmented intervention to support and improve DM Intervention adherence. The overall goal of the PEFI intervention is to help participants find their own motivation to make dietary changes to meet or maintain their fat gram goal. For most participants this means lowering their fat intake. For some participants, this means maintaining their low fat intake. All DM Intervention participants will have the opportunity and encouragement to consider making dietary changes. The process for motivating this dietary change is to have participants complete a self-assessment questionnaire of fat intake (PEFI-Q) and receive computerized tailored feedback based on the questionnaire (PEFI-F). PEFI intervention implementation will be supported primarily through group sessions where participants will complete the self-assessment questionnaire (Summer 2002) and discuss their tailored feedback (Fall 2002). Alternative support may occur through mailings with optional in-person or phone contacts based on existing CC resources and nutritionist discretion. The PEFI intervention and materials were developed by the WHI Dietary Modification Working Group (DMWG), which included representation from the Clinical Coordinating Center (CCC), Lead Nutritionists, Dietary Modification Committee (DMC), Behavioral Advisory Committee (BAC), and Special Populations Advisory Committee (SPAC). PEFI intervention implementation begins June 2002 and continues through November 2002, with data consolidation in February 2003. *Figure 6.16 – PEFI Intervention* provides an overview of the PEFI intervention.

Figure 6.16 – PEFI Intervention



6.15.1 Behavioral Foundation

The behavioral foundation of the PEFI intervention is based upon the principles of motivational enhancement (ME), group facilitation, adult learning, self-assessment, and tailored feedback. The nutritionist uses fundamental skills and key strategies to support and implement these principles throughout the intervention.

The following sections describe these principles, skills, and strategies.

6.15.1.1 Principles

This section describes how the principles of motivational enhancement (ME), group facilitation, adult learning, self-assessment, and tailored feedback are incorporated in the PEFI intervention. Although the principles are listed categorically for emphasis, they are interwoven with each other.

Motivational Enhancement (ME)

Motivational enhancement is incorporated in the PEFI intervention by:

- *Creating an atmosphere* that acknowledges and respects participants' choice and readiness to change. This atmosphere reduces resistance and paves the way for increasing participants' interest in exploring potential change.
- *Empowering participants* to make changes based on choice and readiness – changes that fit for them. Empowering participants supports self-efficacy – their belief that they can succeed and maintain change.
- *Building motivation* by helping participants identify a discrepancy between current and desired fat intake through the use of personalized feedback. Developing discrepancy between where a participant is and where she wants to be creates 'tension' for the participant, leading to increased motivation.

Group facilitation

Group facilitation is incorporated in the PEFI intervention by:

- *Engaging participants* in a way that supports adult learning and enhances group cohesion. Facilitated discussion, exploration and goal setting in a group setting increases active involvement of the participant in the learning process, promotes group cohesion, and supports accountability for making changes.

Adult learning

Adult learning is incorporated in the PEFI intervention by:

- *Identifying participants' existing interests, knowledge, strengths and skills* that support behavior change. Participants become involved and empowered when their interests, knowledge, strengths and skills are recognized, reinforced, and supported.

Self-assessment

The Personalized Evaluation of Fat Intake Self-Assessment Questionnaire (PEFI-Q) and the *Summer 2002 session discussion* form the core self-assessment elements of the PEFI intervention.

- The self-assessment process is important because it creates an opportunity for the participant to have an active role by defining beliefs and expectations about her fat intake. Expressing opinions and expectations increases ownership and responsibility regarding any future behavior change. Ownership and responsibility are important because any information or feedback the participant receives is more likely to be valid in her eyes when she is an active part of the process. This may also set the stage for being more open, in general, to feedback relating to her fat intake. Active involvement in the process also serves to support self-efficacy, the personal belief that one is capable of change.

Tailored feedback

The computerized tailored feedback (PEFI-F) and the *Fall 2002 session discussion* form the core tailored feedback elements of the PEFI intervention.

- Tailored feedback involves receiving personalized information regarding a specific behavior. In the PEFI intervention, the feedback is based on the participant's self-assessment of her fat intake. Receiving tailored feedback allows the participant to reflect upon and be aware of the gap between her present situation and where she would like to be. Awareness of this discrepancy can create 'tension' for the participant, leading to increased motivation.

6.15.1.2 Skills and Strategies

This section describes the fundamental skills and key strategies the nutritionist uses to support and implement the principles guiding the PEFI intervention. The skills are 'learnable abilities' and the strategies are 'techniques'. The skills are necessary to implement the strategies.

Fundamental Skills

- The ability to use open-ended questions, affirmations, reflective listening, and summarizing (OARS).
- The ability to remain directive to the goal while supporting participant choice.
- The ability to facilitate a group discussion by finding the "common threads" among group members, managing group differences, and addressing participant questions.
- The ability to assess and be flexible regarding the varying levels of readiness among participants.
- The ability to manage a variety of emotions, tension, and beliefs relating to the PEFI intervention.

Key Strategies

- Use the participant as a source of expertise and knowledge for herself and for others in the group.
- Provide opportunities to develop and explore the tension created by discrepancy.
- Recognize, reflect, and emphasize participant self-motivational statements (change talk).
- Use tailored feedback to help the participant to identify and explore options for change.
- Provide an opportunity for the participant to develop and share her plan for change.

The Group Nutritionist materials for the Summer and Fall 2002 sessions provide extensive guidelines for delivering these sessions using the principles, skills, and strategies outlined above. Refer to *Vol. 2, Section 6.15.3 – PEFI Implementation* and *Vol. 4, Group Nutritionist Manual, Summer 2002 – Take a Closer Look and Fall 2002 – A Closer Look: What Do I See?*. For additional information, refer to the following WHI resources:

- *ME Corner of the WHI Times dated 1/12/01, 4/27/01, 5/25/01, 6/22/01, 7/27/01* (Outlook Public Folders\All Public Folders\The WHI Times).
- *Volume 2, Appendix G.5 – Motivation Enhancement Training August 1999, WHI Intensive Intervention Protocol.*

6.15.2 PEFI Components

This section describes the Personalized Evaluation of Fat Intake Self-Assessment Questionnaire (PEFI-Q) and the computerized tailored feedback (PEFI-F).

6.15.2.1 PEFI Self-Assessment Questionnaire (PEFI-Q)

The PEFI-Q is a computerized self-assessment tool for dietary fat. The questionnaire provides a view of usual fat intake over the past month. In general, the questionnaire does not ask about foods containing little or no fat, such as fruits and vegetables. It does include reduced-fat and fat-free versions of fat-containing foods.

The role of the PEFI-Q in the PEFI intervention is to provide each participant with a self-assessment opportunity – a chance for each participant to learn more than she already knows about her fat intake. The questionnaire is a supplement to self-monitoring (i.e., not a replacement, not better, not perfect). The questionnaire is not a dietary assessment instrument used to monitor the study.

6.15.2.1.1 Design and Content

The PEFI-Q is a 12-page mark-sense form. It includes a front page and two sections asking about foods.

- The front page includes a place for the participant to write her name, date and group #, and a 'OFFICE USE ONLY' box for CC staff to complete.

- Part I (pages 2-5) – *Usual Food Choices:* consists of 24 adjustment questions that ask about the fat in foods. The questions in this section are used to adjust the information provided on pages 6-12.
- Part II (pages 6-12) – *Usual Food Use:* includes individual food items organized by food groups. This section asks about specific foods: how often they were eaten in the past month and the usual serving size.

Part I (Pages 2-5) – Adjustment Questions

Types of Adjustment Questions

Adjustment questions are used to adjust the amount of fat in the food line items of the questionnaire (pages 6-12). There are two types of adjustment questions used in the PEFI-Q:

- **Frequency of Use:** These questions ask about how often the participant chose a fat-free/low-fat food or how often a mixed dish/soup was prepared to be lower in fat. Examples are shown in *Table 6.6 – Types of Adjustment Questions Used in the PEFI-Q.*
- **Type of Food:** These questions ask about the type of food the participant usually ate. An example is shown in the *Table 6.6 – Types of Adjustment Questions Used in the PEFI-Q*.

Table 6.6 - Types of Adjustment Questions Used in the PEFI-Q

Type of Adjustment Question	Examples
Frequency of Use	Page 2: *Qx. 1 – Did you eat pancakes, waffles or French toast?* *1a – When you ate these foods, how often were they fat-free or low-fat?* Page 5: *Qx. 24 – When you ate mixed dishes or soups, how often were they prepared to be lower in fat?*
Type of Food	Page 3: *Qx. 9 – Did you eat ground meat, ground poultry, or meatless burgers?* *9a – When you ate these foods, what type did you usually eat?* *(Mark all that apply.)*

OPTIONAL READING: *Vol. 2, Appendix G.7.1 – PEFI-Q Adjustment Questions* provides additional information about how the two types of adjustment questions work and the specific line items on the PEFI-Q that are 'adjusted' by the adjustment questions.

Part II (Pages 6-12) – Food Items

Frequency and Serving Size

Frequency choices range from 'Never or less than once a month' to '2+ per day' for food items and '6+ per day' for beverages. The serving size allows the participant to choose between small, medium and large. A medium serving is given as an example on the questionnaire. The PEFI-Q also includes six portion-size graphics (pages 8 and 10) depicting small, medium and large servings for meats and mixed dishes. These graphics are provided to help participants estimate their own usual portion sizes.

Food Line Items

The food items on the PEFI-Q were chosen using the following criteria: a) data-based identification of major contributors of fat in the US diet; b) incorporation of clinical center (CC) suggestions for regional and ethnic foods; and c) incorporation of CC suggestions for low-fat and fat-free modified foods to provide participants the chance to capture dietary changes they have made during the DM Intervention.

It is not possible for the questionnaire to incorporate all the foods that people eat. To include the greatest number of foods for participants, food line items are described in general terms (e.g., *Stews, casseroles or pot pies*), rather than very specific terms. This helps participants identify where their food or mixed dish might fit – instead of looking for a specific food or dish that might not be listed. For example, the foods shown below are not listed on the questionnaire, but they could fit under the following 'general' line items:

- *Beef stroganoff* – fit under the mixed dish line item – *Stews, casseroles or pot pies.*
- *Fudgesicles* – fit under the line item – *Frozen desserts (all types).*

Equivalency Help Sheet:

A number of ethnic-specific dishes were included based on input from clinical centers with diverse populations. Examples: foods added within the existing line items (e.g., *potted or canned meat* added to existing line item 44) or foods added as specific line items (e.g., new line item 56 includes *Egg rolls, lumpia, dim sum (fried varieties), or cone sushi with fried tofu wrap)*. In addition, clinical centers have the option to develop Equivalency Help Sheets for their ethnically-diverse populations, if they feel that there are some frequently-consumed high-fat food items that are not included on the questionnaire.

Before developing an Equivalency Help Sheet, the Lead Nutritionist considers the following:
- Is the food or mixed dish already on the PEFI-Q?
- Is the food or mixed dish a major contributor of fat for participants?

The Lead Nutritionist creates an Equivalency Help Sheet that includes only foods that are major contributors of fat for participants, and only foods that are not already on the PEFI-Q. An Equivalency Help Sheet that provides too much (or necessary information could confuse or frustrate some participants.

Figure 6.17 – Template: Equivalency Help Sheet for Local Foods provides a sample template that CCs could use when developing an Equivalency Help Sheet.

Figure 6.17 – Template: Equivalency Help Sheet for Local Foods

The PEFI self-assessment questionnaire was developed for Dietary Change participants across the United States. So, you may not be able to find some of the foods that are special to our area of the country. Below, we have listed some local favorites and indicated where you might mark them on the questionnaire. If you cannot find a food that you frequently eat, please ask your nutritionist for help.

Local Food	Where to Mark Questionnaire	Page
Grain Products and Salty Snacks		
Meat, Poultry, Fish and Eggs		
Fats Used at the Table or Added in Cooking		
Mixed Dishes and Soups		
Milk, Cheese and Yogurt		
Sweets		
Milk as Beverages		

6.15.2.1.2 Quality Control

The goal for the quality control measures for the PEFI-Q is to balance the quality of tailored participant feedback with the amount of staff time needed to follow-up on incomplete questionnaires. Two types of measures comprise the quality control: defaults for missing information and errors that prevent analysis.

6.15.2.1.2.1 Defaults for Missing Information

Defaults are used when responses to adjustment questions are missing or inconsistent with the associated line item. Defaults are also used when serving sizes are missing.

Adjustment Question Defaults: The defaults used for PEFI-Q adjustment questions are based on food choices analyzed from AV1 FFQs of Dietary Change participants. There are two types of defaults used: 'frequency of use' and' type of food'. Examples of adjustment question defaults are outlined on the following page.

Adjustment Question (Examples)	Default Used if Adjustment Question Not Answered (Examples)
Frequency of use: - *Qx. 2a – When you ate these breads, how often were they fat-free or low-fat?* - *Qx. 10a – When you ate beef, pork, ham, or lamb, how often did you eat the fat?*	Frequency of use: - *Sometimes* - *Rarely*
Type of food: - *Qx. 9a – When you ate these foods, what type did you usually eat? (Mark all that apply.)* - *Qx. 13a – When you used fat at the table, what kind of fat did you usually use? (Mark all that apply.)*	Type of food: - *Extra lean* - *Butter, margarine, olive or other oil*

If a default is used, the computer programming will use the fat grams assigned to the default to calculate total fat, but the food will not be included in the participant's top 10 foods listed on Page 3 of the PEFI-F. For example:

- PEFI-Q marked this way: If for Qx. 45 (pg. 8) a participant marks that she ate a medium serving of *All types of ground meat or ground poultry* – once a week, but she does not complete the associated adjustment question (Qx. 9a, pg. 3) – *When you ate these foods, what type did you usually eat?*),
- Result: The computer will use the fat grams assigned to the default (extra lean) to calculate total fat, but the food – 'Ground meat or ground poultry' will not appear in the participant's list of top 10 foods on the PEFI-F.

When an adjustment question default is used, a warning message appears on the *PEFI Scanning Results* report. For information about warning messages, refer to the PEFI Upgrade Notes (Outlook Public Folders\All Public Folders\WHILMA Resources\PEFI Upgrade Notes).

Serving Size Default: If a participant does not mark a serving size, a "medium" serving will be used as the default.

OPTIONAL READING: *Vol. 2, Appendix G.7.1 – PEFI-Q Adjustment Questions* provides more information about the how defaults work and specific defaults that are used for each adjustment question when information is missing.

6.15.2.1.2.2 Errors that Prevent Analysis

If any of the following errors occur, the PEFI-Q will not be analyzed:

- Missing 'OFFICE USE ONLY' information (Qxs. 1-6)
- An entire page of questionnaire not completed.
- More than 5 questions missing on pages 2-4.
- More than 3 items missing for Qx. 24 (pg. 5).
- More than 31 food line items missing on pages 6-12.

When an error prevents analysis, an error message appears on the *PEFI-Q Scanning Results* report. For information about error messages refer to the PEFI Upgrade Notes (Outlook Public Folders\All Public Folders\WHILMA Resources\PEFI Upgrade Notes).

6.15.2.2 Tailored Feedback (PEFI-F)

Participants completing the PEFI-Q receive a packet of computerized tailored feedback (PEFI-F). The information in the PEFI-F is tailored for the participant based on her responses on the PEFI-Q. The role of the PEFI-F in the PEFI intervention is to provide the participant with tailored feedback about her dietary fat intake. The tailored feedback sets the stage for building motivation to consider dietary change to meet (or maintain) fat gram goal. Refer to *Vol. 2, Section 6.15.1 (including subsections) – Behavioral Foundation.*

Note: The Summer and Fall 2002 session materials refer to the PEFI-F as 'personalized information' and 'PEFI packet' rather than 'tailored feedback' and 'PEFI-F'. This was done to use more participant-friendly wording.

Design and Content

The PEFI-F sets the stage for building motivation to consider dietary change by prompting the participant to explore the following: her fat intake compared to her fat gram goal, her sources of dietary fat (food groups and foods), and options for dietary change that she would consider making. The participant's fat grams reported on the PEFI-Q determine the PEFI-F's dietary change focus according to the following three fat gram categories:

- **Participants over fat gram goal:** receive a PEFI-F that focuses on reducing fat intake.
- **Participants ≤ fat gram goal, but ≥ 15 grams of fat:** receive a PEFI-F that focuses on maintaining fat intake, or making changes (to reduce fat) if they seem right.
- **Participants < 15 grams of fat:** receive a PEFI-F that focuses on exploring how closely the information matches what the participant eats and making changes if they seem right. The changes considered likely depend on how closely the information matches what the participant eats. Examples of changes to consider: to change amount of fat – increase or decrease; to change type of fat; etc. Refer to *Vol. 2, Section 6.15.4.2.3 – Managing Participants Who Report <15 Grams of Fat.*

The PEFI-F includes four pages plus a cover page. A brief description of each page follows immediately below. *Table 6.7 – Summary of PEFI-F Pages* provides a detailed description of each page of the PEFI-F as determined by the participant's fat grams reported on the PEFI-Q. Refer to *Vol. 2, Appendix G.7.3 – PEFI-F Samples* to see a sample PEFI-F for each of the three fat gram categories listed above. *Vol. 4, Group Nutritionist Manual, Fall 2002 – A Closer Look: What Do I See?* provides additional information about what each page prompts the participant to think about as she explores her tailored feedback.

Cover Page – *Your Personalized Evaluation of Fat Intake*
The cover page provides privacy and allows the participant to control whether others see her tailored feedback. The cover page includes the participant's name and the date the PEFI-Q was completed.

Page 1 – *Where Are You in Relation to Your WHI Fat Gram Goal?*
Page 1 provides a comparison of the participant's fat grams reported on the PEFI-Q and her fat gram goal. This is illustrated two ways: a bar graph and arithmetically. For participants above fat gram goal per the PEFI-Q, this page also includes a comparison of fat grams over goal per day and per week (using a second bar graph). The participant's fat grams reported on the PEFI-Q (see the three fat gram categories above) determine the text at the bottom of this page.

If a negotiated fat gram goal is used for the PEFI intervention, it is reflected on this page. Refer to *Vol. 2, Section 6.15.4.2.2 – Managing Participants with a Negotiated Fat Gram Goal* for information about using a negotiated fat gram goal in the PEFI intervention.

Page 2 – *Where Does Your Dietary Fat Come From?*
Page 2 shows the participant's distribution of fat grams reported on the PEFI-Q by food group. This is illustrated using a pie chart that shows the percent (%) of fat contributed by each food group. This page also points out the two food groups providing the most fat.

Page 3 – *Top Ten Foods That Provide Fat in Your Diet*
Page 3 shows the participant's top 10 sources of fat reported on the PEFI-Q, including the number of fat grams each provides per week. The top 10 fat sources are listed in order from highest to lowest fat grams. This page also offers tailored ideas for lower-fat choices for each of the top 10 foods and shows fat gram savings per week if the lower-fat choices were used. The participant's fat grams reported on the PEFI-Q (see the three fat gram categories above) determine the text at the top and bottom of this page.

OPTIONAL READING: For information about how the tailored low-fat message ideas for each of the top 10 foods are determined, refer to *Vol. 2, Appendix G.7.2 – Tailored Messages for Top Ten Foods on PEFI-F.*

Page 4 – *Next Steps: Where Do You Go From Here?*

Page 4 provides space for the participant to develop a list of change options she might consider. The participant's fat grams reported on the PEFI-Q (see the three fat gram categories above) determine the content of this page. Participants over fat gram goal or ≤ fat gram goal, but ≥ 15 grams of fat receive a page that provides structure to identify options for change to reduce fat intake. Participants <15 grams of fat receive a page that encourages a meeting with the nutritionist to explore the feedback further and provides space for the participant to think about the following: how closely the very low fat intake matches what she eats, whether any high-fat foods may have been missed on the PEFI-Q, and whether she is interested in making changes in what she eats. Refer to *Vol. 2, Section 6.15.4.2.3 – Managing Participants Who Report <15 Grams of Fat.*

Implementation

Refer to the following WHI Manual references for additional information about the PEFI-F: *Vol. 2, Section 6.15.3.2 – Fall 2002 (9F) Maintenance Session* and *Vol. 4, Group Nutritionist Manual, Fall 2002 – A Closer Look: What Do I See?*.

Table 6.7 – Summary of PEFI-F Pages

Page	Page Heading	Fat Grams Reported on PEFI		
		over fat gram goal	**≤ fat gram goal, but ≥ 15 grams fat**	**< 15 grams fat**
Cover Page	Your Personalized Evaluation of Fat Intake (PEFI)	• Cover sheet with participant name and date questionnaire completed. • Provides general information about what is in packet. • Informs participant that the Fall session will provide an opportunity to discuss the PEFI feedback. • Thanks participant.	Same	Same
Page 1	Where Are You in Relation to Your WHI Fat Gram Goal?	Two graphs: • Fat grams reported on PEFI compared to fat gram goal • Fat grams OVER goal (per day and per week) Text next to graph: Points out difference in fat grams between fat gram goal and fat grams reported on PEFI. Text at bottom: Prompts participant to: • Think about ways she could begin to reduce weekly fat intake. • Look at how even small changes can make a big difference.	One graph: Fat grams reported on PEFI compared to fat gram goal Text next to graph: Points out that fat intake is AT or BELOW her fat gram goal. Text at bottom of page: Prompts participant to: • Think about how closely the information matches what she eats. • Consider how she might use the information to maintain current fat intake, or make some changes if they seem right.	One graph: Fat grams reported on PEFI compared to fat gram goal Text next to graph: • Points out that estimated fat intake is very low. • Encourages participant to talk with her nutritionist to explore the information further. Text at bottom of page: Prompts participant to: • Think about how closely the information matches what she eats. • Consider how she could use the information to make some changes, if they seem right.
Page 2	Where Does Your Dietary Fat Come From?	Pie chart: % of fat contributed by each food group Text: • Points out the two food groups providing the most fat in the participant's diet. • Prompts participant to go to next page.	Same	Same

Table 6.7 – Summary of PEFI-F Pages (Cont.)

Page	Page Heading	Fat Grams Reported on PEFI		
		over fat gram goal	**≤ fat gram goal, but ≥ 15 grams fat**	**< 15 grams fat**
Page 3	Top Ten Foods that Provide Fat in Your Diet	Text at top: There are many different ways that you can reduce your fat intake. Below are some ideas for lower-fat choices. Top 10 fat sources: • Food (serving size & frequency) • Fat grams per week • Lower fat choices • Fat gram savings per week Text at bottom: Circle the foods she might change.	Same	Text at top: Based on your responses on the PEFI self-assessment questionnaire, your fat intake appears to be very low. Think about whether any of these ideas for lower-fat choices seem right for you. Top 10 fat sources: • Same Text at bottom: • None
Page 4	Next Steps: Where Do You Go From Here?	Text at top: Look at the foods you circled on page 3. Use the statements below to help you think about as many ideas for change as you wish. Then, consider which changes you might make. Remember…the choice is yours! Changes to consider: • Reduce portion. • Change frequency. • Cut back on fat used to prepare or cook food. • Choose a low-fat or fat-free food instead of regular full-fat choice. • Other Idea: _____	Same	Text at top: Based on your responses on the PEFI self-assessment questionnaire, your estimated fat intake is very low. Consider asking yourself the questions below to help you think about your eating pattern. Questions: • How closely does this very low fat intake match what I eat? • Are there any high-fat foods that I missed recording on my PEFI self-assessment questionnaire? If yes, high-fat foods I missed? How often do I eat these foods? • Am I interested in making some changes in what I eat? If yes, what changes might I consider? Examples provided. Text at bottom: We encourage you to talk with your nutritionist to explore your personalized information further.

6.15.3 PEFI Implementation

The PEFI intervention uses the existing Dietary Change group session structure. The Summer and Fall 2002 sessions work together to accomplish the goal of the PEFI intervention. Participants complete the PEFI-Q at the Summer 2002 (8SU) session and receive computerized tailored feedback (PEFI-F) at the Fall 2002 (9F) session. Alternative support may occur through mailings with optional in-person or phone contacts based on existing CC resources and nutritionist discretion. Refer to *Vol.2, Section 6.15.4.2.1 – Managing Participants Who Complete 8SU and/or 9F by Mail or Phone.*

6.15.3.1 Summer 2002 (8SU) Session

The overall goal of the Summer 2002 (8SU) session is to build participant interest in a) completing the PEFI-Q and b) receiving computerized tailored feedback about dietary fat intake based on the information provided in the questionnaire. This will be accomplished by providing an opportunity for the participant to:

- discuss the benefits of self-assessing and receiving tailored feedback about fat intake,
- complete the PEFI-Q, and
- explore expectations about the information she might receive about her dietary fat intake.

The discrepancy segment in this session is designed to help the participant see a possible 'gap' in awareness of her fat intake. Acknowledging a gap in awareness of fat intake can build interest in completing the PEFI-Q and receiving tailored feedback. The session materials strive to keep balance between building interest in the PEFI-Q and maintaining interest and perceived value in on-going self-monitoring. The materials accomplish this by a) presenting PEFI-Q as something to supplement self-monitoring (i.e., not a replacement, not better, not perfect) and b) acknowledging the critical role that participant self-monitoring plays in being aware of fat intake and meeting (or maintaining) fat gram goal. *Table 6.8 – Summer 2002 (8SU) Session* summarizes the key points for each session component. The Group Nutritionist session materials provide extensive guidelines for delivering the session using motivational enhancement, group facilitation skills, and adult learning principles. Refer to *Volume 4, Group Nutritionist Manual, Summer 2002 – Take a Closer Look.*

6.15.3.2 Fall 2002 (9F) Session

The overall goal of the Fall 2002 (9F) session is to guide and support the participant's efforts to develop a plan for meeting (or maintaining) her fat gram goal. This will be accomplished by providing an opportunity for the participant to:

- become more aware of fat intake by receiving tailored feedback based on the PEFI-Q,
- build motivation to meet (or maintain) her fat gram goal by exploring tailored feedback to identify possible discrepancy between current and desired fat intake, and
- develop a plan for meeting (or maintaining) her fat gram goal after identifying and exploring options for dietary change.

The session materials strive to empower the participant by creating an atmosphere that acknowledges and respects participant choice and readiness. The materials accomplish this by providing the opportunity for the participant to a) generate thoughts and statements about the value of awareness, b) explore her tailored feedback and compare her 'expectations' about what PEFI-F may tell her to what PEFI-F 'actually' tells her, and c) possibly find motivation to make (and share her plan for) dietary change. The discrepancy segment in this session is designed to build motivation by helping the participant see a possible 'gap' in current vs. desired fat intake. This segment builds on the discrepancy segment in the 8SU session. Helping the participant see a gap in awareness of fat intake and then a gap in her fat intake can help move her along the continuum of change. *Table 6.9 – Fall 2002 (9F) Session* summarizes the key points for each session component. Note: An activity is included for participants who do not have a PEFI-F available, thus supporting their full participation in the session. Refer to *Volume 2, Section 6.15.4.2.4 – Managing Participants Who Attend 9F, but Do Not Have PEFI-F.* The Group Nutritionist session materials provide extensive guidelines for delivering the session using motivational enhancement, group facilitation skills, and adult learning principles. Refer to *Volume 4, Group Nutritionist Manual, Fall 2002 – A Closer Look: What Do I See?.*

Table 6.8 – Summer 2002 (8SU) Session

Session Component	Key Points
Group Sharing/Next Steps Follow-Up Purpose: To build group cohesion and participant self efficacy.	The focus of the **Group Sharing/Next Steps Follow-Up** component for this session is limited to brief group sharing (for group cohesion and bonding). Limiting the focus of this segment helps maximize the amount of time available (later in the session) for completing the PEFI-Q.
Setting the Stage for Skill Building Purpose: To identify participant's interest and needs for skill building.	The focus of the **Setting the Stage for Skill Building** component is to: a) briefly outline the skill building segments and b) assess participant relative interest in the segments. Assessing relative interest in the segments enables the nutritionist to acknowledge and support participant interest while including all segments.
Skill Building Purpose: To provide opportunities for life-relevant discussion and/or practice.	Each of the segments in the **Skill Building** component builds on the previous. All parts together form the foundation for completing the PEFI-Q. Therefore it is important to include each segment. The amount of time devoted to each segment will be determined by a) the amount of time needed to complete the PEFI-Q and b) participant interest in each segment relative to the others. Building Interest: The intent of the first segment is to help the participant identify possible discrepancy between where she perceives her current fat intake and where she would like her fat intake to be, as well as how closely self-monitoring fat scores represent her fat intake. A participant worksheet (*Worksheet 1 – A Closer Look)* supports this segment. The second segment provides an opportunity for participants to discuss the benefits of knowing what you eat when working toward or maintaining fat gram goal. The sequential discussion of discrepancy and then benefits builds interest by providing an opportunity for the participant to come to (some or all of) the following conclusions: • *I see a difference between where I am (or where the study is) and where I would like to be in terms of fat intake.* • *I see that there may be a difference between my self-monitoring fat scores and my fat intake.* • *For me to meet or maintain my fat gram goal, I need to know as much as I can about my fat intake.* • *I would like to complete the PEFI Self-Assessment Questionnaire so that I'll receive personalized information that might help me learn even more than I already know about my fat intake.* PEFI-Q: The second half of the session focuses on completing the PEFI-Q. This should take approximately 30-40 minutes.
Next Steps Purpose: To increase the likelihood that participants will apply session information and skills.	The **Next Steps** component focuses on briefly exploring expectations about the information that may come from completing the questionnaire. The exploration of expectations is supported by a participant worksheet (*Worksheet 2 – My Expectations*). This segment is intended to a) increase participant anticipation and excitement about receiving personalized information from the PEFI self-assessment questionnaire and b) increase participant ownership of the information.
Food Tasting Purpose: To increase the likelihood that participants will use recipes and food that support WHI goals.	The **Food Tasting** component provides participants with the opportunity to taste low-fat foods that support WHI goals.

Table 6.9 – Fall 2002 (9F) Session

Session Component	Key Points
Group Sharing/Next Steps Follow-Up Purpose: To build group cohesion and participant self efficacy.	The focus of the **Group Sharing/Next Steps Follow-up** component for this session is to: a) have the nutritionist very briefly recap key points from the previous session and then b) have participants revisit the concept of awareness (of fat intake) also discussed in the previous session. Having participants share and discuss 'how being more aware of fat intake can help meet (or maintain) fat gram goal' sets the stage (and continues to build interest) for the rest of the session where participants receive and explore their personalized information about fat intake.
Setting the Stage for Skill Building Purpose: To identify participant's interest and needs for skill building.	The focus of the **Setting the Stage for Skill Building** component is to: a) briefly outline the skill building segments and b) assess participant relative interest in the segments. Assessing relative interest in the segments enables the nutritionist to acknowledge and support participant interest while including all segments.
Skill Building Purpose: To provide opportunities for life-relevant discussion and/or practice.	Each of the segments in the **Skill Building** component builds on the previous. All segments together form the foundation for the participant to identify options and a plan for dietary change to meet (or maintain) fat gram goal. Therefore it is important to include each segment. The amount of time devoted to each segment will be determined by participant interest in each segment relative to the others. Receive Personalized PEFI Packet: The overall intent of this segment is to build participant awareness of her dietary fat intake. The segment has two parts: a) brief orientation to the packet and b) review of the personalized content. This segment provides an opportunity for the participant to become familiar with and understand the content of the packet through brief orientation and discussion. Build Discrepancy: This segment provides an opportunity for the participant to explore thoughts and feelings about her fat intake. The intent of this segment is to help the participant identify possible discrepancy between where she sees her fat intake and where she would like her fat intake to be. *Worksheet 2 – My Expectations* (completed during the 8SU session) supports this segment. Identify Options & Plan**:** This segment provides an opportunity for the participant to identify options for change in a step-wise fashion. First, she'll have the opportunity to develop a list of possible options. Then she'll have the chance to narrow the options to the few that she might consider over the next ~3 months. Finally, she'll have the chance to select the one option she sees herself most likely doing in the near future and create a plan for making it happen. The intent of this segment is to help the participant prepare for dietary change.
Next Steps Purpose: To increase the likelihood that participants will apply session information and skills.	The **Next Steps** component provides an opportunity for the participant to share her personalized plan for dietary change in an atmosphere that acknowledges and respects personal choice and readiness. *Worksheet 1 – My Plan* provides the framework for the discussion. This segment emphasizes public disclosure of intended behavior change – as a way to help the participant strengthen her awareness of and commitment to the intended change she's identified.
Food Tasting Purpose: To increase the likelihood that participants will use recipes and food that support WHI goals.	The **Food Tasting** component provides participants with the opportunity to taste low-fat foods that support WHI goals.

6.15.4 PEFI Management

This section describes policies and procedures for managing PEFI intervention operations.

6.15.4.1 Lead Nutritionist Responsibilities

The Lead Nutritionist oversees management of the following PEFI intervention operations:

- Sample
- Staffing
- Participant Materials Management
- Implementation
- Intervention Issues

Sample. All DM Intervention participants are eligible to participate in the PEFI intervention.

The PEFI intervention is designed for implementation within Dietary Change group sessions and, therefore, is anticipated to be offered primarily to participants having active DM Intervention participation status. Refer to *Vol. 2, Section 6.10.6.2.2 – Active Participation* for the definition of active DM Intervention participation status.

Offering the PEFI intervention to participants having inactive DM Intervention participation status (i.e., marked 'stop' DM Intervention on *Form 7 – Participation Status*) is optional per CC discretion and staffing resources. The Lead Nutritionist uses procedures outlined in *Vol. 2, Section 6.15.4.2.1 – Managing Participants with Stop DM Intervention Status* when opting to include inactive participants in the PEFI intervention.

Staffing. As noted in previous sections, the PEFI intervention is designed for implementation within Dietary Change group sessions. Therefore, the Lead Nutritionist applies usual staffing configurations for delivery of this intervention and works with the Clinic Manager to determine which staff (within the CC) are best suited to scan the PEFI-Q and generate the computerized tailored feedback (PEFI-F). Refer to *Section 6.15.5* (including all subsections) – *PEFI Data Processing* for information about scanning the PEFI-Q and generating PEFI-F.

If staffing resources permit, the Lead Nutritionist may want to consider having the Group Nutritionist plus a second staff person (who is familiar with the PEFI-Q) at the Summer 2002 group session. The second staff person's main role would be to review the completed PEFI-Qs for missing items while the Group Nutritionist facilitates the remaining portion of the session (i.e., *Next Steps* component). The in-session review of the questionnaires could maximize efficiency by eliminating the need to follow-up on missing items after the session. Refer to *Vol. 2, Section 6.15.2.1.3 – Quality Control* for information about Quality Control measures for the PEFI-Q.

Participant Materials Management. The PEFI-Q and Summer 2002 (8SU) participant materials are designed to be given to the participant at the same time and, ideally, in a group setting. The same is true for the PEFI-F and the Fall 2002 (9F) participant materials. To support delivery of the PEFI intervention as designed, the Lead Nutritionist is strongly encouraged to use the procedures outlined below when offering these materials to participants:

1. Do not mail these materials to participants at the beginning of the quarter (i.e., before they have had the opportunity to attend a group session).
2. Offer these materials when participants attend the group session.
3. Mail these materials to individual participants when the nutritionist knows the participant will not be attending the session. Use the makeup procedures outlined in *Vol. 2, Section 6.15.4.2.5 – Managing Participants Who Complete 8SU and/or 9F by Mail or Phone.*

Implementation. The Lead Nutritionist manages local PEFI intervention implementation. To guide Lead Nutritionist efforts, the DMWG (with support and approval of the DMC) developed definitions and goals for completion. The completion definitions apply to the PEFI sessions (8SU and 9F) and the overall PEFI intervention. The completion goals apply to the PEFI sessions.

Completion Definitions:

Completion of the 8SU and 9F sessions is not dependent on completing the PEFI-Q. Similarly, the PEFI intervention can be completed by a route other than the 8SU and 9F sessions (e.g., individual contact). Refer to *Vol. 2, Section 6.15.4.2.5 – Managing Participants Who Complete 8SU and/or 9F by Mail or Phone.* The definitions outlined below support routes for session and PEFI intervention implementation that are flexible and inviting for the participant.

- 8SU completion: Participants attending or making up 8SU will be considered to have completed the session; completion of the PEFI-Q is not required for 8SU completion. Example: A participant who completes the session (in-person or by mail) but declines to complete the questionnaire will be considered to have completed 8SU.
- 9F completion: Participants attending or making up 9F will be considered to have completed the session; completion of the PEFI-Q and/or receiving the PEFI-F is not required for 9F completion. Example: A participant who completes the session (in-person or by mail) will be considered to have completed 9F even if she did not complete the PEFI-Q and/or receive a PEFI-F.
- PEFI intervention completion: Participants having a scannable PEFI-Q that produces a PEFI-F will be considered to have completed the PEFI intervention. Receipt and discussion of the PEFI-F is assumed and documentation is not tracked or required centrally. PEFI intervention completion does not require 8SU or 9F session completion.

Completion Goals:

There are no protocol-mandated completion goals for the PEFI intervention or sessions. However, the DMWG (with support and approval of the DMC) recognizes the value of having goals to work toward for implementation. Therefore, the Lead Nutritionist at each center is encouraged to establish CC-specific implementation goals that encourage local nutritionists to stretch slightly beyond session completion rates for the Summer and Fall 2001 sessions (i.e., 7SU and 8F). The Lead Nutritionist is encouraged to establish realistic goals (e.g., ~5% above the Summer and Fall 2001 completion rates). These goals will be for local use only, and will not be used for CC or studywide monitoring.

The Lead Nutritionist tracks PEFI intervention implementation progress using WHILMA resources outlined in *Section 6.15.6 – WHILMA Resources for PEFI Tracking.*

Intervention Issues. The Lead Nutritionist oversees management of interventions issues as described in *Section 6.15.4.2* (including all subsections*) – Intervention Issues.*

6.15.4.2 Intervention Issues

The Lead Nutritionist manages intervention issues as outlined below.

6.15.4.2.1 Managing Participants with 'Stop' DM Intervention Status

If staffing resources permit and the Lead Nutritionist determines that the PEFI-Q could be a useful tool for discussing re-engagement, the PEFI intervention may be offered to participants having inactive DM Intervention participation status (i.e., marked 'stop' DM Intervention on *Form 7 – Participation Status*). Refer *to Vol. 2, Section 6.15.4.1 – Responsibilities (Sample).* **Important note:** A participant having inactive DM Intervention participation status should not be approached for the PEFI intervention if she has 'Absolutely No Contact' follow-up status on *Form 7 – Participation Status*.

Inactive participants who complete the PEFI-Q should be reinstated to active DM Intervention status (i.e., marked 'active' DM Intervention on *Form 7 – Participation Status*). These participants are no longer refusing all contact with the Group Nutritionist and other CC nutrition staff. Refer to *Vol. 2, Section 6.10.6.2 – Definition of Non-Participation and Active Participation*.

6.15.4.2.2 Managing Participants with a Negotiated Fat Gram Goal

Many participants who received the higher fat gram goals early in the trial (29 - 37 grams) have volunteered to strive for a "negotiated" fat gram goal that is lower than their assigned fat gram goal. Additionally, some participants having extreme difficulty meeting their assigned fat gram goal have negotiated with their nutritionist to strive for a slightly higher goal. The PEFI intervention has been designed to recognize and support the efforts of participants who have negotiated with their nutritionist to strive for a fat gram goal that is different than their assigned fat gram goal.

If a participant has been working toward a negotiated fat gram goal prior to the start of the PEFI intervention, this goal may be used to tailor the computerized feedback generated from the PEFI-Q. This should not be a goal established specifically for the PEFI intervention, nor should it be a goal established without participant involvement.

To use a negotiated fat gram goal for the PEFI intervention, the nutritionist records the negotiated fat gram goal in the 'OFFICE USE ONLY' box on the PEFI-Q as outlined in *Vol. 3, Forms, Instructions for Form 73 – PEFI Self-Assessment Questionnaire*. When the questionnaire is analyzed, the negotiated fat gram goal will be used instead of the assigned fat gram goal to determine the tailored feedback for the PEFI intervention. Only the negotiated fat gram goal will appear in the PEFI-F for the participant; there is no mention of her assigned fat gram goal. **Important note:** Using the negotiated fat gram goal for the PEFI intervention does NOT change the assigned fat gram goal in the WHILMA database.

6.15.4.2.3 Managing Participants Who Report <15 Grams of Fat

Participants reporting fat intake <15 grams/day on the PEFI-Q receive tailored feedback encouraging them to meet with their nutritionist to explore the feedback further. The tailored feedback also prompts the participant to begin exploring the feedback on her own. Refer to *Vol. 2, Section 6.15.2.2 – Tailored Feedback* for a complete description of the information given to participants reporting <15 grams/day.

An individual meeting (in-person or phone) occurs after the participant's initial exploration of her personalized feedback, if she and the nutritionist determine that an individual meeting would be helpful. The purpose of the individual meeting would be to help the participant continue exploring how closely the estimated very low fat intake matches what she eats, whether any high-fat foods may have been missed, and possible next steps for dietary change. A discussion of next steps for dietary change will likely be influenced by the participant's perception of how closely the <15 gram/day intake represents what she eats. The following paragraphs provide some guidelines for what might occur in an individual meeting, based on the participant's perception of how closely the <15 gram/day intake represents what she eats (i.e., not close or close).

Not Close to What She Eats

If a participant determines that her estimated very low fat intake of <15 grams/day on the PEFI-Q is not close to what she typically eats, she and the nutritionist could explore whether any high-fat foods may have been missed and which foods these may have been. The participant's list of missing high-fat foods could be used to generate discussion about next steps for dietary change as outlined on the *Next Steps: Where Do You Go From Here?* page of the participant's PEFI-F. **Important note:** If the participant is considering changes to reduce her fat intake, she may find it helpful to use a *Next Steps* page that provides more structure for changes to reduce fat intake. The *Next Steps* page in the *A Closer Look* packet can be used for this purpose. Refer to *Vol. 4, Group Nutritionist Manual, Fall 2002 Session, Group Nutritionist Resource 1 – Managing Participants Without a Personalized PEFI Packet*.

If a participant determines that her estimated fat intake is very low because she was eating atypically during the month captured in the questionnaire (e.g., illness), she and the nutritionist could explore whether any high-fat foods may have been missed and which foods these may have been. A discussion of next steps for dietary change, as described for the scenario above, could follow this exchange. Alternatively, the participant could (if she's interested) add the missing foods to her PEFI-Q and have it re-scanned. If the participant chooses this option, use procedures for re-scanning the "PEFI 1 Contact" outlined in the PEFI Upgrade Notes (Outlook Public Folders\All Public Folders\WHILMA Resources\PEFI Upgrade Notes).

Close to What She Eats

If a participant determines that her estimated very low fat intake of <15 grams/day on the PEFI-Q is close to what she typically eats, then she and the nutritionist could explore the participant's interest in making dietary changes as outlined on the *Next Steps: Where Do You Go From Here?* page of the participant's PEFI-F. This exploration of interest could include an assessment of her very low fat eating pattern as described in *Vol. 2, Section 6.13 – Guidelines for Participants Self-Reporting Scores Consistently <15 grams/day.* Pending the participant's interest in making some changes in what she eats, a discussion of next steps for dietary change could follow this exchange. A discussion of possible dietary changes would likely focus on changes to increase variety and balance in food choices and fat sources, and could also include discussion of possible changes to increase fat intake. There is no expectation that a participant whose estimated fat intake is very low (<15grams/day) would further reduce her fat intake.

6.15.4.2.4 Managing Participants Who Attend 9F, but Do Not Have PEFI-F

It is possible that a participant attending the Fall 2002 (9F) session will not have a PEFI-F to receive at the session. The most likely scenario for this happening will be the hard-to-reach participant who arrives unexpectedly at the 9F session without having completed the 8SU session and/or the PEFI-Q. If a participant arrives at the 9F session and the nutritionist does not have a PEFI-F for her, the primary goal is to facilitate this participant's involvement in the session discussion and activities. The nutritionist facilitates this involvement by offering a brief self-assessment instrument that is completed during the session. Refer to *Vol. 4, Group Nutritionist Manual, Fall 2002 Session, Nutritionist Resource 1 – Managing Participants Without a Personalized PEFI Packet*. **Important note**: If the participant would like to complete the PEFI-Q, the nutritionist works with the participant after the session to arrange this. The participant should not complete the questionnaire during the session. Completing the questionnaire during the session would prohibit the participant from joining the discussion and activities.

6.15.4.2.5 Managing Participants Who Complete 8SU and/or 9F by Mail or Phone

Nutritionists use the procedures outlined below to manage participants who complete 8SU and/or 9F by mail or phone. For related information, refer to *Vol. 2, Section 6.15.4.1 – Responsibilities (Participant Materials Management* and *Implementation).*

The nutritionist initiates the mail or phone makeup process when she knows the participant will not be attending the session. For some participants, this will be at the beginning of the quarter (e.g., participants who are traveling or otherwise away from the CC). For some participants, this will be during the quarter (e.g., participants who miss their group session and know at that time that they won't be able to attend another group). For many participants, this will be at the end of the quarter (e.g., participants who have not attended or completed the session by the time all group sessions have been offered).

The nutritionist initiates the mail or phone makeup process by sending the participant the materials outlined below.

8SU

Materials to send for 8SU makeup:

- The *Summer 2002 – Take A Closer Look* participant materials.
- The *Makeup for Summer 2002 Group Session* sheet (see *Vol. 4, Group Nutritionist Manual, Summer 2002 Session*).
- A copy of the PEFI-Q (unless Not Applicable or Refused completing the questionnaire).
- Self-monitoring tools, as appropriate.
- A self-addressed stamped envelope.

Documenting 8SU session completion:

The nutritionist documents (in WHILMA using *Form 64 – Individual Data Sheet*) completion of the session when any of the following occur:

- The participant returns the completed *Makeup for Summer 2002 Group Session* sheet and completed PEFI-Q.
- The participant returns only the completed *Makeup for Summer 2002 Group Session* sheet.
- The participant returns only the completed PEFI-Q.
- The participant and nutritionist discuss the session via telephone and the discussion includes dialogue related to the questions on the *Makeup for Summer 2002 Group Session* sheet. Important note: Do not have the participant complete the PEFI-Q over the phone.

Suggestion for 8SU makeup by phone:

Begin by asking the participant to share her thoughts (and questions) about the session materials. As part of the discussion, guide the participant to respond to the three questions outlined on the *Makeup for Summer 2002 Group Session* sheet.

9F

Materials to send for 9F makeup:

- The *Fall 2002 – A Closer Look: What Do I See?* participant materials.
- The *Makeup for Fall 2002 Group Session* sheet (see *Vol. 4, Group Nutritionist Manual, Fall 2002 Session*).
- The participant's PEFI-F packet (or *A Closer Look* packet if she doesn't have a PEFI-F).
- Self-monitoring tools, as appropriate.
- A self-addressed stamped envelope.

Documenting 9F session completion:

The nutritionist documents (in WHILMA using *Form 64 – Individual Data Sheet*) completion of the session when any of the following occur:

- The participant returns the completed *Makeup for Fall 2002 Group Session* sheet.
- The participant and nutritionist discuss the session via telephone and the discussion includes dialogue related to the questions on the *Makeup for Fall 2002 Group Session* sheet.

Suggestion for 9F makeup by phone:

Begin by asking the participant to share her thoughts (and questions) about the session materials. If the participant has a PEFI-F to explore, use the text in the participant session materials as a guide for discussion. As part of the discussion, guide the participant to respond to the three questions outlined on the *Makeup for Fall 2002 Group Session* sheet.

6.15.4.2.6 Managing Participants Who Are Guests from a Different Clinical Center

Participants sometimes attend Dietary Change group sessions as a guest at a different clinical center. When this occurs, the participant's data cannot be entered at the 'guest CC' and must be sent back to the 'home CC' for processing. Nutritionists use the procedures outlined below to manage participants who complete the 8SU and/or 9F sessions at a guest CC.

Guest at 8SU

1. The nutritionist from the home CC contacts the nutritionist at the guest CC to arrange the specific Dietary Change group that the participant will attend.
2. The participant attends at the guest CC and completes the session activities, including completing the PEFI-Q.
3. The nutritionist at the guest CC does the following: a) documents the participant's interactions during the session on a Progress Note, b) collects any self-monitoring tools she brought to the session, c) collects her completed PEFI-Q and *Worksheet 1 – My Expectations*, d) reviews the PEFI-Q for completeness (making changes as needed before the participant leaves the session), and e) sends the collected materials to the

home CC nutritionist for data entry and processing. The nutritionist at the guest CC does not record the participant's attendance on any DM Intervention data collection forms.

4. The nutritionist at the home CC receives the materials above and does the following: a) documents session completion on *Form 64* (including a note on the form indicating that the participant attended the session at the guest CC), b) scans the PEFI-Q and c) prints the PEFI-F. If the participant will be attending 9F at her home CC, then the nutritionist follows procedures as usual. If the participant will be attending 9F at the guest CC, then both nutritionists use the procedures outlined below.

Guest at 9F

1. The nutritionist from the home CC contacts the nutritionist at the guest CC to arrange the specific Dietary Change group that the participant will attend.
2. The nutritionist from the home CC sends the nutritionist at the guest CC a copy of each of the following: a) the participant's completed PEFI-Q (i.e., in case the participant has questions about what she marked on the questionnaire), b) the participant's PEFI-F; c) the participant's completed *Worksheet 1 – My Expectations* and d) any Progress Notes related to the 8SU session.
3. The participant attends at the guest CC and completes the session activities, including receiving her PEFI-F. If the participant did not complete the PEFI-Q, then the nutritionist at the guest CC uses procedures outline in *Vol. 2, Section 6.15.4.2.4 – Managing Participants Who Attend 9F, but Do Not Have PEFI-F*.
4. The nutritionist at the guest CC does the following: a) documents participant's interactions during the session on a Progress Note (including what she shares as her plan for dietary change), b) collects any self-monitoring tools she brought to the session, and c) sends the collected materials (including the PEFI-Q, if at the guest CC) to the home CC nutritionist for data entry and processing. The nutritionist at the guest CC does not record the participant's attendance on any DM Intervention data collection forms.
5. The nutritionist at the home CC receives the materials above and documents session completion on *Form 64* (including a note on the form indicating that the participant attended the session at the guest CC).

6.15.4.2.7 Managing Participants with Adherence and Retention Challenges

The WHI Adherence and Retention Working Group (A&R WG) conducted a survey of all WHI staff during Fall 2001 to identify common adherence and retention challenges. This survey resulted in an extensive list of challenges categorized by study arm. The survey and results can be found in the Outlook Public Folders (OutlookPublicFolders\A&R Resources\Survey Results.Summary and Survey Results.DM). The A&R WG and DMWG developed suggestions for managing the common challenges identified for DM Intervention participants during PEFI implementation. These suggestions emphasize utilizing existing resources to manage challenges in a manner that is flexible, supportive, and inviting for participants. Refer to *Table 6.10 – Suggestions for PEFI Implementation in Response to A&R Survey.*

Table 6.10 – Suggestions for PEFI Implementation in Response to A&R Survey

Approved by DMWG Dec 18, 2001

A&R Survey-Identified Challenge	Suggestion for PEFI Implementation
AGE POOR VISION LOW LITERACY	• Try to have an additional WHI staff member attend the 8SU session to help women complete the PEFI-Q. • For 8SU mail make-up (which may include completing the questionnaire), suggest that a family member or friend read the questions out loud and mark the participant's responses.
TRANSPORTATION	• Arrange transportation for women who need rides – either taxies, vans or buddy rides. • Complete the PEFI-Q by mail (as part of 8SU make-up). Follow-up by phone per available resources.
DECLINING SESSION ATTENDANCE	• Sponsor "bring a group member" to PEFI session – play up as special session – DON'T MISS IT. • Encourage women to attend a session even if not with their own group. • Arrange session make-up in conjunction with a clinic visit. • If missed 8SU, mail PEFI-Q (as part of make-up) and follow-up with phone call encouraging 9F attendance.
SELF-MONITORING (FATIGUE, BURN-OUT, or NOT DOING)	• Be sensitive to and acknowledge those women who do not self-monitor so they will not feel pressured or guilty. • Engage these women in all aspects of 8SU and 9F discussions. See the numerous *Nutritionist Notes* and *Group Facilitation Suggestions* in the GN Facilitation Outlines for these sessions.
NOT MEETING GOALS	• Be sensitive to and acknowledge those women who have not been meeting their fat goal so they will not feel pressured or guilty. • Engage these women in all aspects of 8SU and 9F discussions. See the numerous *Nutritionist Notes* and *Group Facilitation Suggestions* in the GN Facilitation Outlines for these sessions.
FAMILY DEMANDS LIFESTYLE	• During 9F, help participants consider and explore challenges (e.g., family demands or illness, lifestyle conflicts, or eating out/social events) as they identify their options and plan for meeting (or maintaining) their fat gram goal.
NEED MORE INDIVIDUAL CONTACT TO ADDRESS INDIVIDUAL DIFFERENCES	• Allow women the chance to stay after sessions to discuss specific problems they are having. • Call participants as needed and per available resources.

6.15.5 PEFI Data Processing

The following section describes the procedures for processing the PEFI self-assessment questionnaire (PEFI-Q) and generating the tailored feedback (PEFI-F).

6.15.5.1 Collection, Review, and Processing of the PEFI-Q

The PEFI-Q is a scannable mark-sense form. The Lead Nutritionist works with the Clinic Manager to determine which staff (within the CC) are best suited to scan the PEFI-Q and generate the PEFI-F.

PEFI-Q Collection and Review

Ideally, the PEFI-Q is briefly reviewed before the participant leaves the Summer 2002 (8SU) session. This review may be done by a nutritionist or other designated staff. *Section 6.15.4.1 – PEFI Management (Staffing*) provides suggestions for how this review could be accomplished during the 8SU session.

The purpose of the brief review is to catch obvious errors, such as blank pages or multiple marks, and then to have the participant make the necessary changes before leaving the session. Guidelines for this cursory review and pre-scan edit are provided in *Vol. 3 – Forms, Instructions for Form 73 – PEFI Self-Assessment Questionnaire* and the PEFI Upgrade Notes (Outlook Public Folders/All Public Folders/WHILMA Resources/PEFI Upgrade Notes).

Before scanning the PEFI-Q, the nutritionist (or designated staff) completes the questions in the 'OFFICE USE ONLY' box. A description and item instructions for each of these questions (1-7) are provided in *Vol. 3 – Forms, Instructions for Form 73 – PEFI Self-Assessment Questionnaire*. There are two questions in the 'OFFICE USE ONLY' box that are unique to the PEFI intervention:

- Question 6 (PEFI Contact) is used to distinguish the PEFI-Q completed as part of the PEFI intervention from any subsequent PEFI-Qs. The PEFI-Q completed for the PEFI intervention is marked 'PEFI 1'.
- Question 7 (FGG) is used to capture a participants 'negotiated fat gram goal'. This is an optional field and should be marked ONLY if the participant has a negotiated fat gram goal. Refer to *Section 6.15.4.2.2. – Managing Participants with a Negotiated Fat Gram Goal* for information about using a negotiated fat gram goal in the PEFI intervention.

After the PEFI-Q has been reviewed and the questions in the 'OFFICE USE ONLY' box have been completed, the questionnaire is ready for scanning.

PEFI-Q Scanning

Ideally, the PEFI-Q is scanned as soon as possible after the Summer 2002 (8SU) session to provide the Lead Nutritionist with the most up-to-date information for PEFI implementation tracking. Refer to *Vol. 2, Section 6.16.6 – WHILMA Resources for PEFI Tracking.* As noted in previous sections, participants receive their PEFI-F at the Fall 2002 (9F) session. The ~3-month timeframe between the Summer and Fall sessions provides ample time for the nutritionist (or designated staff) to review and scan the questionnaire, correct errors (if necessary), and generate the PEFI-F.

The PEFI-Q is scanned in the same way as other WHI mark-sense forms. Procedures describing how to scan the PEFI-Q are provided in the PEFI Upgrade Notes. If needed, additional information about scanning mark-sense forms can be found in *Vol. 5 – Data System, Section 7.2.1.1. – Some Tips for Successful Scanning* and *Section 7.2.2. – Scanning a Mark-Sense Form*.

Clinical centers (CCs) may find it helpful to scan the PEFI-Q in batches according to DM group, one group at a time. This will make it easy to:

- Review the scanning results by DM group. The *PEFI-Q Scanning Results* report for the batch will apply to participants in a single DM group. This will be particularly important if the CC has determined that each nutritionist reviews the *PEFI-Q Scanning Results* report for participants in her own DM groups.
  - If participants from multiple groups are scanned together, multiple copies of the *PEFI-Q Scanning Results* report may be needed to complete the review (i.e., a copy for each nutritionist reviewing the results of the batch).
- Print copies of the PEFI-F for participants in a batch. If all participants in a given scanning batch are in the same DM group, printing the PEFI-F for all participants in the batch can be accomplished simply by printing the PEFI-F for the entire DM group.
  - If participants from multiple DM groups are scanned together, printing the PEFI-F for all participants in the batch requires that the PEFI-F be printed for each group in the batch, or for each participant individually.

Reviewing the PEFI-Q Scanning Results Report

The *PEFI-Q Scanning Results* report automatically appears on the WHILMA screen after a batch of PEFI-Qs has been scanned. This report shows the scanning result for each PEFI-Q in the batch. The possible scanning results include: 'Accepted', 'Accepted with warnings', and 'Failed'. The staff person responsible for scanning the PEFI-Qs gives a copy of the *PEFI-Q Scanning Results* report, along with the batch of scanned PEFI-Qs, to the nutritionist (or designated staff) to review. Refer to the PEFI Upgrade Notes for information about error and warning messages that appear on the *PEFI-Q Scanning Results* report. For information about errors that prevent PEFI-Q analysis and defaults that are used when responses to PEFI-Q adjustment questions are missing, refer to *Vol. 2, Section 6.15.2.1.2 – Quality Control.*

By reviewing the *PEFI-Q Scanning Results* report, the nutritionist (or designated staff) is able to:

- Identify PEFI-Qs that have a 'Failed' result and contact participants, as necessary, to capture missing information.
- Review the warning messages for PEFI-Qs that have an 'Accepted with warnings' result. This review provides the nutritionist with information about the amount of tailoring in the participant's PEFI-F. If time and staff resources permit, the nutritionist has discretion to follow-up with the participant to clarify warning messages (e.g., inconsistent or missing responses) and, thereby, maximize tailoring of the PEFI-F.

Re-Scanning the PEFI-Q

The PEFI-Q is re-scanned if changes are made after the initial scanning (e.g., after correcting errors or after discretionary follow-up on warnings). When a PEFI-Q is re-scanned (i.e., the same booklet number passes through the scanner), the existing PEFI data, including PEFI-F, is overwritten. For more information about how WHILMA handles the data when a PEFI-Q is re-scanned, refer to the PEFI Upgrade Notes.

Note:

- Each participant can have only one PEFI-Q that is completed as part of the PEFI intervention (i.e., Qx. 6 – PEFI Contact marked 'PEFI 1').
- If a participant's 'PEFI 1' questionnaire needs to be replaced instead of re-scanned (i.e., a different booklet number), use the procedures in the PEFI Upgrade Notes. This situation will be very rare. Example: The participant's 'PEFI 1' questionnaire has a scanning result of 'Accepted with warnings'. When the nutritionist reviews the PEFI-Q, it is somehow damaged to the point that it cannot be re-scanned. The nutritionist completes a different booklet (marked 'PEFI 1') to replace the damaged 'PEFI 1' questionnaire.

Storing the PEFI-Q

The nutritionist stores the scanned PEFI-Q with the participant's DM Intervention file or in an easily retrievable manner.

6.15.5.2 Generating Tailored Feedback (PEFI-F)

When the PEFI-Q is successfully scanned, it is automatically analyzed and the data necessary to generate the PEFI-F are stored in WHILMA. Refer to *Vol. 2, Section 6.15.2.2 – Tailored Feedback (PEFI-F)* for a complete description of the PEFI-F.

Printing PEFI-F

The PEFI-F can be generated and printed any time after the PEFI-Q has been successfully scanned. There are many printing options for the PEFI-F. These include:

- Printing multiple copies. This option gives the nutritionist the ability to print a copy of the PEFI-F that will be given to the participant as well as a copy to keep in the participant's DM Intervention file.
  - It may be most efficient to print two copies of the PEFI-F as soon as the analysis is complete. Consider storing the copies of the PEFI-F with the PEFI-Q in the participant's DM Intervention file or in an easily retrievable manner.

- If a center has many participants completing sessions by guest attendance, it may be helpful to develop a plan in advance of the Fall 2002 (9F) session to ensure that the nutritionist has ready access to the PEFI-F of participants who attend as a guest.

- Printing select copies. The PEFI-F may be printed using a number of different selection parameters (e.g., for an individual, for a specific DM group, by language [English or Spanish]).
  - The option to print the PEFI-F by "individual or group" gives the nutritionist flexibility to print the PEFI-F for all participants in a specified group or a single individual. The nutritionist will most often print the PEFI-F by group. The option to print for an individual could be useful when a participant completes the Fall 2002 (9F) session by guest attendance (at a group other than her own) or when she completes makeup by mail.
  - The option to print the PEFI-F in English or Spanish gives the nutritionist flexibility to provide a participant with a Spanish language PEFI-F if that is the participant's preference. The copy for the participant's file can be printed in English or Spanish per the nutritionist's preference.

  Note:

  - The PEFI-F cannot be printed by scanning batch. See the information above regarding scanning the PEFI-Q in batches by DM group.
  - The PEFI-F cannot be printed in color (as a result of Oracle software programming limitations).

For more information about printing the PEFI-F and using the different print parameters, refer to the PEFI Upgrade Notes.

6.15.6 WHILMA Resources for PEFI Tracking

This section describes the WHILMA resources for PEFI tracking. This includes the *PEFI Tracking Screen* and the *PEFI Contact 1 Tracking* report. Supporting information can be found in the PEFI Upgrade Notes (Outlook Public Folders/All Public Folders/WHILMA Resources/PEFI Upgrade Notes).

6.15.6.1 PEFI Tracking Screen

The *PEFI Tracking Screen* enables the nutritionist to key-enter optional data for tracking PEFI intervention implementation. The optional data includes:

- Date PEFI-Q Provided
- Date PEFI-F Provided
- Reason PEFI Not Completed

Date PEFI-Q Provided (Optional)

The 'Date PEFI-Q Provided' field represents the date the PEFI-Q was provided to the participant. There are at least two ways that this optional field could be used:

- Use for all participants who are provided the PEFI-Q.
  - For participants who are provided the PEFI-Q at the 8SU session, the date of the 8SU session would be the 'Date PEFI-Q Provided'.
  - For participants who are provided the PEFI-Q by mail, the date the PEFI-Q was mailed to the participant would be the 'Date PEFI-Q Provided'.
- Use for only those participants who are provided a PEFI-Q by mail. This could help the nutritionist quickly distinguish participants who may need follow-up to collect the PEFI-Q from those who attended the 8SU session (and, therefore, likely completed and turned-in their questionnaire during the session).
  - For participants who attend the 8SU session, the nutritionist would leave the 'Date PEFI-Q Provided' field blank.
  - For participants who are provided the PEFI-Q by mail, the date the PEFI-Q was mailed to the participant would be the 'Date PEFI-Q Provided'.

Date PEFI-F Provided (Optional)

The 'Date PEFI-F Provided' field represents the date the PEFI-F was provided to the participant. This field could be used in a manner similar to that described above for 'Date PEFI-Q Provided'.

- Use for all participants who are provided a PEFI-F.
  - For participants who are provided the PEFI-F at the 9F session, the date of the 9F session would be the 'Date PEFI-F Provided'.
  - For participants who are provided the PEFI-F by mail, the date the PEFI-F was mailed to the participant would be the 'Date PEFI-F Provided'.
- Use for only those participants who are provided the PEFI-F by mail. This could help the nutritionist quickly distinguish participants who may need follow-up to discuss the PEFI-F from those who attended the 9F session (and, therefore, likely received their PEFI-F during the session).
  - For participants who attend the 9F session, the nutritionist would leave the 'Date PEFI-F Provided' field blank.
  - For participants who are provided the PEFI-F by mail, the date the PEFI-F was mailed to the participant would be the 'Date PEFI-F Provided'.

If a clinical center chooses to not track the optional data outlined above, the Summer 2002 (8SU) and Fall 2002 (9F) session information can be used as a marker that participants have received the PEFI-Q and PEFI-F. Refer to *Vol. 2, Section 6.15.6.2 – PEFI Contact 1 Tracking Report (Implementation Tracking).*

Reason PEFI Not Completed (Optional)

The 'Reason PEFI Not Completed' field represents the reason that the participant did not complete the PEFI-Q. Options include: Not appropriate, Declined, Not reached. Examples of how to select 'Reason PEFI Not Completed':

- *Not appropriate:* The nutritionist selects and enters this option when her/his clinical judgement indicates that the participant should not be approached to complete the PEFI-Q. This decision may occur because a participant has a crisis situation (e.g., serious personal or family illness, the death of spouse, etc.).
- *Declined:* The nutritionist selects and enters this option when the participant is offered, but declines to complete the PEFI-Q.
- *Not reached:* The nutritionist marks this option when her/his clinical judgement indicates that the participant cannot be reached to complete the PEFI-Q (e.g., the participant does not return a PEFI-Q that was provided by mail).

Data Entry in the PEFI Tracking Screen

If a clinical center chooses to enter optional data (described above) in the *PEFI Tracking Screen*, staff have two options for completing the data entry:

- Use direct data entry (i.e., enter the information without hard copy documentation).
- Document the optional data on a hard copy tracking sheet before the information is key-entered. This option may be particularly useful at clinical centers where nutritionists do not perform their own data entry. *Figure 6.18 – Sample PEFI Tracking Sheet* provides an example tracking sheet that nutritionists may use.

How the PEFI Tracking Screen Links to the PEFI Contact 1 Tracking Report

The *PEFI Tracking Screen* lists all Dietary Change participants, except those who are deceased. Active participants assigned to a DM group are listed by their group number. Active participants who are not assigned to a DM group and inactive participants (i.e., marked 'stop' DM Intervention on *Form 7 – Participation Status*) are listed in the 'unassigned' category.

- For active participants, optional data that are entered in the *PEFI Tracking Screen* appear on the *PEFI 1 Contact Tracking* report.
- For inactive participants, optional data that are entered in the *PEFI Tracking Screen* do not appear on the *PEFI 1 Contact Tracking* report. Inactive participants who complete the PEFI-Q should be reinstated to

active DM Intervention status (i.e., marked 'active' DM Intervention on *Form 7 – Participation Status*). Refer to *Vol. 2, Section 6.15.4.2.1 – Managing Participants with Inactive DM Intervention Status*.

Figure 6.18 – Sample PEFI Tracking Sheet

Nutritionist ID: _____ Group #: _____	ID: __ __ __ __ - ___ ___ ___ - __ First Name _____M.I._____ Last Name _____

1. Date PEFI-Q provided: ☐☐-☐☐-☐☐
   Month Day Year

2. Date PEFI-F provided: ☐☐-☐☐-☐☐
   Month Day Year

3. Reason PEFI not completed:
   ☐1 Not appropriate
   ☐2 Declined
   ☐3 Not reached

6.15.6.2 PEFI Contact 1 Tracking Report

The Lead Nutritionist (or designee) uses the *PEFI Contact 1 Tracking* report *(PEFI 0001)* to track local implementation of the PEFI intervention in active DM Intervention participants. The report shows data for only the following:

- The 'PEFI 1' contact. This is the PEFI-Q completed as part of the PEFI intervention. For a complete description of the 'PEFI 1' contact, refer to *Vol. 3 – Forms, Instructions for Form 73 – PEFI Self-Assessment Questionnaire.*
- Active DM Intervention participants. For information about tracking inactive DM Intervention participants in the PEFI intervention, refer to *Volume 2, Section 6.15.6.1 – PEFI Tracking Screen (How the PEFI Tracking Screen Links to the PEFI Contact 1 Tracking Report).*

Implementation Data

The *PEFI Contact 1 Tracking* report captures all aspects of PEFI intervention implementation. For each participant listed, the report provides the following information:

- *Summer Scheduled:* the scheduled date for the participant's 8 Summer (8SU) session.
- *Summer Completed:* the date the participant completed the 8SU session.
- *PEFI-Q Provided*: the date the PEFI-Q was provided to the participant (optional data; shown if entered in the *PEFI Tracking Screen).*

- *Latest PEFI 1 Event*: information about the latest PEFI 1 event. This includes questionnaire scanning status, analysis completion, and printing PEFI-F.
- *Latest PEFI 1 Event Date*: the date of the latest PEFI 1 event.
- *Reason PEFI Not Completed*: the reason the participant did not complete the PEFI-Q (optional data; shown if entered in the *PEFI Tracking Screen*). Options include: Not appropriate, Declined, and Not reached.
- *9 Fall Scheduled:* the scheduled date for the participant's 9 Fall (9F) session.
- *9 Fall Completed:* the date the participant completed the 9F session.
- *PEFI-F Provided:* the date the PEFI-F was provided to the participant (optional data; shown if entered in the *PEFI Tracking Screen).*

Implementation Tracking

The Lead Nutritionist (or designee) uses the *PEFI Contact 1 Tracking* report to track the following:

- Participants who have had the opportunity to begin the PEFI intervention. This can be tracked using the *8 Summer Scheduled* and *8 Summer Completed* columns.
- Participants who have received a PEFI-Q. This can be tracked two ways:
  - Use the *Date PEFI-Q Provided* column if this optional data item has been entered in the *PEFI Tracking Screen*.
  - Use the *8 Summer Completed* column as a marker for receiving PEFI-Q; i.e., assume that the participant received PEFI-Q if she completed the session.
- Participants who have completed a PEFI-Q. This can be tracked using the *Latest PEFI 1 Event* and *Latest PEFI 1 Event Date* columns.
  - Use the *Reason PEFI Not Completed* column for additional information, if this optional data item has been entered in the *PEFI Tracking Screen*.
- Participants who have received their PEFI-F. This can be tracked two ways:
  - Use the *Date PEFI-F Provided* column if this optional data has been entered in the *PEFI Tracking Screen.*
  - Use the *9 Fall Completed* column as a marker that the participant received her PEFI-F; i.e., assume that the participant received her PEFI-F if she completed the session.

It is recommended that the Lead Nutritionist run the *PEFI Contact 1 Tracking* report monthly.

Using the PEFI Contact 1 Tracking Report

The *PEFI Contact 1 Tracking* report has many parameters that allow data to be sorted and filtered. The default sort order for the report lists groups by nutritionist in order of their 8SU scheduled date. This sort order can be changed to list groups by nutritionist in order of group number or by the 9F scheduled date. Refer to the PEFI Upgrade Notes for a complete description of parameters for this report.

Below are two simple examples of how parameters can be used to sort and filter the *PEFI Contact 1 Tracking* report.

- Tracking overall implementation progress

  1. Run the *PEFI Contact 1 Tracking* report from the WHILMA report menu.
  2. Leave all parameters as they appear on the screen.

  This version of the report lists all groups by nutritionist in order of the 8SU scheduled date. Within each group, participants are listed alphabetically by name. This provides an overall picture of PEFI implementation by nutritionist (i.e., all groups and all participants within each group) sorted in the order you would expect participants to begin PEFI activities. Sorting the report this way helps distinguish groups (and participants) that have started the PEFI intervention from those that have not yet started.

- Tracking participants who have received the PEFI-Q

  Note: This example applies only if the optional data for 'Date PEFI-Q Provided' have been entered in the *PEFI Tracking Screen*.

  1. Run the *PEFI Contact 1 Tracking* report from the WHILMA report menu.
  2. PEFI-Q Provided: Choose "Yes".

  This report lists only those participants who have a 'Date PEFI-Q Provided' in WHILMA. Participants are listed in order by nutritionist and group. For each participant listed, you can track the status of the PEFI-Q by looking at the Latest PEFI 1 Event column. This will allow you to identify participants who have a successfully scanned and analyzed PEFI-Q, those with a PEFI-Q that needs follow-up, those who have had their PEFI-F run (printed), and those who do not yet have a PEFI 1 event (i.e., PEFI 1 Event column blank). Filtering the report this way helps narrow the tracking focus.

6.15.7 Scientific Issues

This section addresses two scientific issues related to the PEFI intervention: bias and evaluation.

1. Bias refers to the possibility that women exposed to the PEFI-Q and PEFI-F will provide more socially desirable responses to subsequent WHI FFQs.
2. Evaluation refers both to monitoring protocol completion and to evaluating the effect of the PEFI intervention on the C-I.

The paragraphs below describe each of these issues in detail.

Bias in Dietary Self-report

A legitimate concern regarding the PEFI intervention is the possibility that completion of the PEFI-Q, and receiving the PEFI-F, will bias subsequent dietary self-report in DM Intervention women. Specifically, the hypothesis is that women exposed to the PEFI intervention will provide more socially desirable responses to WHI FFQs used for trial monitoring. If such social desirability bias did occur, it would result in a widening of the C-I that would not be distinguishable from real changes in dietary behavior. The WHI Steering Committee considered the issue of bias when it approved the PEFI intervention and felt that the benefit to the trial justified the potential risk to trial monitoring activities (i.e., the C-I as estimated by the WHI FFQ).

There are two major reasons why the potential for dietary self-report bias associated with the PEFI intervention was deemed an acceptable "risk":

- The potential for introducing social desirability bias already exists in the self-monitoring tools and the dietary change program materials. Therefore it is not clear that the PEFI intervention will significantly increase intervention-associated bias above what already exists.
- The WHI DM is a randomized controlled trial with disease outcomes and therefore bias in dietary self-report cannot threaten the integrity of the main trial results.

There will likely be secondary analyses of diet-disease relationships in the WHI DM trial. However, most of these analyses will rely on "baseline" (i.e., AV1) dietary data that are already collected. Therefore any intervention-associated bias introduced by the PEFI intervention does not threaten these types of diet-disease analyses.

Evaluation of the PEFI Intervention

The evaluation of the PEFI Intervention has two components:

1. Monitor completeness of the protocol implementation.
2. Estimate effect of the PEFI intervention on change in percent energy from fat in Dietary Change participants using the WHI FFQ.

Completeness of the protocol implementation

The PEFI intervention is of relatively short duration. Therefore it will not be feasible to monitor ongoing protocol implementation, although a final report on the completion rates for the PEFI intervention will be prepared after conclusion of the intervention. This report will show protocol completeness studywide and by CC. In addition, the *PEFI Contact 1 Tracking Report (PEFI0001)* will be available to allow CCs to track PEFI intervention implementation. However this CC report is for operational support rather than performance evaluation.

Effect of the PEFI intervention on change in percent energy from fat in Dietary Change participants

The CCC will conduct a before-and-after analysis using data from the AV-1 FFQ and FFQs completed during the PEFI intervention. Specifically, we can compare participants who completed an FFQ before receiving the PEFI intervention (i.e., a PEFI control group) with participants who completed an FFQ after receiving the PEFI intervention (i.e., a PEFI intervention group). The outcome variable will be change in percent energy from fat from AV-1 to the most recent FFQ and the model will be controlled for potential covariates such as age, race/ethnicity, education, visit year, and clinic effects. These data permit a pairwise analysis of the effect of the PEFI intervention on Dietary Change participants' fat intake in the "PEFI control" vs. "PEFI intervention" groups. The sample sizes should provide a reliable studywide estimate, but are too small to provide precise clinic-specific estimates of the PEFI intervention effect.

The PEFI intervention protocol, as implemented in WHI, is not designed for a rigorous test of the effectiveness of this augmented intervention in reducing fat intake for the following reasons: variability in administration, concurrent effects of the main intervention, and lack of an appropriate comparison group.

6.16 Personalized Evaluation of Fat Intake 2003 (PEFI 2003)

The PEFI 2003 intervention is a self-help version of the original PEFI intervention with the overall goal of supporting and improving DM Intervention adherence. This intervention offers self-guided materials to help participants find their own motivation to make dietary changes to meet or maintain their fat gram goal. All interested DM Intervention participants will have the opportunity to complete PEFI 2003. For many participants this will be their second PEFI intervention. PEFI 2003 implementation begins September 2003 and continues through January 2004 with data consolidation in February and May 2004. The PEFI 2003 materials are modeled after the original PEFI intervention materials. Refer to *Vol. 2, Section 6.15 – Personalized Evaluation of Fat Intake (PEFI)*.

6.16.1 PEFI 2003 Components

This section describes PEFI 2003 components: PEFI-Q Cover Letter/Instructions, PEFI-Q (ver. 2), PEFI-F, and Guide for Your PEFI Packet.

6.16.1.1 PEFI-Q Cover Letter/Instructions

The PEFI-Q Cover Letter/Instructions will be mailed with the PEFI self-assessment questionnaire (PEFI-Q ver. 2). The PEFI-Q Cover Letter/Instructions is a brief (2-page) document. It has three main goals: a) to offer participants the opportunity to complete the questionnaire, while emphasizing the voluntary nature of this activity, b) to provide key tips to help participants complete the questionnaire, and c) to highlight potential problem areas for participants to check before returning their completed questionnaire. The information provided in the PEFI-Q Cover Letter/Instructions is intentionally brief to encourage reading. Refer to *Vol. 2, Appendix G.8.2., Figure G.4* to see a sample of the PEFI-Q Cover Letter/Instructions.

6.16.1.2 PEFI-Q (ver. 2)

The PEFI-Q (ver.2) is almost identical to the PEFI-Q used in the original PEFI intervention. Modifications were made in the text of a few adjustment questions and line items to improve clarity and participant understanding (e.g., adding the words "diet lean" to the ground meat adjustment; adding "tuna fish" to the fish line items). Changes to the PEFI-Q database were considered (e.g., changes in fat grams and serving sizes), however, no objective data were available to evaluate the impact of the suggested edits on data accuracy and comparability between the original PEFI-Q and PEFI-Q (ver. 2). Therefore, no changes were made in the database. For detailed information about the design and content of the PEFI-Q, refer to *Vol. 2, Section 6.15.2.1 – PEFI Self-Assessment Questionnaire (PEFI-Q).*

Quality Control Measures

The goal for the quality control measures for the PEFI-Q (ver. 2) is to balance the quality of the tailored feedback with the amount of staff time needed to follow-up on incomplete questionnaires. This goal is unchanged from the original PEFI-Q. Two types of measures comprise the quality control: defaults for missing information and errors that prevent analysis.

Defaults for Missing Information

The defaults used for *PEFI-Q (ver. 2)* are unchanged from the original PEFI-Q. For information, refer to *Vol. 2, Section 6.15.2.1.2.1 – Defaults for Missing Information*.

- Central (CCC) Administration: The CCC will use defaults when responses to adjustment questions are missing or inconsistent with the associated line item.
- Local (CC) Administration: CCs will have the option to use defaults or to contact participants to clarify items generating a warning message.

Errors that Prevent Analysis

The errors that prevent analysis of the PEFI-Q (ver. 2) are unchanged from those used for the original PEFI-Q. For additional information, refer to *Vol. 2, Section 6.15.2.1.2.2 – Errors that Prevent Analysis*. The following procedures are used to reduce the number of PEFI-Q (ver.2) errors.

Central (CCC) Administration:

- Provide the PEFI-Q Cover Letter/Instructions that prompts the participant to review her questionnaire for blank pages and unanswered questions on pages 2-5.
- Use programming defaults to complete the information required in the "Office Use Only" box on the PEFI-Q (ver. 2).

Local (CC) Administration:

- Provide the PEFI-Q Cover Letter/Instructions that prompts the participant to review her questionnaire for blank pages and unanswered questions on pages 2-5.
- Review the completed PEFI-Q (ver. 2) before scanning to ensure the items in the "Office Use Only Box" are appropriately completed.

6.16.1.3 PEFI-F

Participants completing the PEFI-Q (ver. 2) will receive a packet of computerized tailored feedback (PEFI-F). The PEFI-F for PEFI 2003 is a modified version of the original PEFI-F. Some text was modified to support the self-help nature of the PEFI 2003 and to enhance participant acceptance of the materials. The most significant change was made to the < 15 grams of fat packet. This packet no longer includes ideas for lower fat choices.

The participant's fat grams reported on the PEFI-Q determine the PEFI-F's dietary change focus according to the following three fat gram categories: 1) participants over fat gram goal receive a PEFI-F that focuses on **meeting** fat gram goal; 2) participants $\leq$ fat gram goal, but $\geq$ 15 grams of fat receive a PEFI-F that focuses on **maintaining** fat gram goal; and 3) participants < 15 grams of fat receive a PEFI-F that focuses on **exploring** how closely the information matches what the participant eats and making changes if they seem right for her. Refer to *Vol. 2, Appendix G.8.2., Figures G.6, G.7, and G.8* to see a sample PEFI-F for each of the three fat gram categories.

6.16.1.4 Guide for Your PEFI Packet

The Guide for Your PEFI Packet will be mailed with the participant's PEFI-F. The brief (2-page) guide orients the participant to each page of her PEFI-F and provides a few questions for thought as she explores her tailored feedback. Refer to *Vol. 2, Appendix G.8., Figure G.9* to see a sample of the Guide for Your PEFI Packet.

6.16.2 PEFI 2003 Implementation

Participation is optional for Clinical Centers and participants. CCs may choose to implement PEFI centrally (CCC) or locally (CC) or not at all. The Lead Nutritionist uses the *PEFI 2003 Mailing Selection Screen* to designate which participants will receive PEFI 2003 and how the intervention will be delivered (i.e., centrally or locally). Refer to *Section 6.16.3.1 – PEFI Mailing Selection Screen*. To support participant self-empowerment, nutritionists are not expected to discuss the PEFI-F with participants, although they are encouraged to be available to discuss questions received from individual participants.

6.16.2.1 Central (CCC) Administration of PEFI 2003

During September to November 2003, the CCC will mail the following materials to DM Dietary Change participants designated to receive PEFI 2003 centrally: PEFI-Q Cover Letter/Instructions; PEFI-Q (ver.2); self-addressed return envelope; and a pencil. Approximately one-third of participants will receive the questionnaire and accompanying materials each month. During October 2003 to January 2004, the CCC will scan the questionnaire and mail the PEFI-F with the Guide for Your PEFI Packet to participants. Participants

will receive their tailored feedback within approximately four weeks of CCC receipt of the completed questionnaire. The CCC will accept and process completed questionnaires through March 31, 2004.

PEFI Failures:

- Follow Up for First PEFI Failure:
  If a PEFI-Q (ver. 2) fails (i.e., cannot be analyzed), the CCC will return the questionnaire to the participant with a return envelope. A letter (PEFI-Q Request for Additional Information) will accompany the questionnaire, explaining why the form is being returned and listing the pages that the participant needs to check and complete before returning the questionnaire (i.e., missing or lightly marked circles). A sample of the letter is included in *Vol. 2, Appendix G.8, Figure G.5.*

- Follow Up for Second PEFI Failure:
  If a PEFI 2003 questionnaire fails a second time, a printed message (i.e. Second Failure) will appear on the *PEFI Tracking Report* so that the local nutritionist can follow up with the participant. Nutritionists can contact their CCC Nutrition Liaison to request the participant's failed PEFI-Q. Refer to the PEFI 2003 Upgrade Notes. (Outlook Public Folders/All Public Folders/WHILMA Resources/PEFI 2003 Upgrade Notes.)

Printing the PEFI-F

CCs will be able to print the PEFI-F for centrally scanned PEFI-Qs (ver. 2). Refer to the PEFI 2003 Upgrade Notes.

6.16.2.2 Local (CC) Administration of PEFI 2003

Clinical Center nutrition staff determine how participants will receive the PEFI materials (e.g., by mail or in-person) and monitor the intervention using the *PEFI 2003 Tracking Report*. Refer to *Section 6.16.3.4 - PEFI 2003 Tracking Report.*

The CCC will use the information from the *PEFI 2003 Mailing Selection Screen* to determine the quantity of materials required to support CCs who choose local implementation. These materials include: PEFI-Q (ver. 2); PEFI-Q Cover Letter/Instructions; Guide for Your PEFI Packet, and pencils. CCs implementing PEFI 2003 locally will be able to scan the PEFI-Q (ver. 2) at their CC and print the PEFI-F and PEFI Request for Additional Information letter. (Refer to the PEFI 2003 Upgrade Notes). CCs are responsible for all administrative costs associated with local implementation (e.g. distribute and scan PEFI-Q (ver. 2); print PEFI-F; postage, envelopes, participant mailing and identification labels etc.). All CCs will receive a small supply of PEFI 2003 materials described above.

PEFI 2003 Reminder Postcard

A PEFI 2003 Reminder Postcard is available for use with all PEFI 2003 participants at CC discretion.

- The postcard provides a reminder to return the completed questionnaire. CCs opting to use the postcard will send it to the participant approximately two weeks after her PEFI-Q (ver.2) has been mailed. Refer to *Section 6.16.3.4 - PEFI 2003 Tracking Report* for information about tracking when the questionnaire is mailed.

- The postcard is located in the Outlook Public Folders/All Public Folders/Manual Information/CC Print Materials. CCs opting to use the postcard will print it from the Outlook Public Folders. Printing and postage for the postcard are at CC expense.

- The postcard was developed by the Lead Nutritionist Regional Chairs (LNRCs) and approved by Participant Material Review at the CCC. CCs opting to modify the postcard (or use a different postcard) should submit the revised (or new) postcard to Participant Material Review at the CCC per usual procedure.

Review and Processing of PEFI-Q (ver. 2)

The procedures for scanning PEFI-Q and generating PEFI-F are similar to those used for the original PEFI intervention. For guidelines about reviewing the completed PEFI-Q, refer to *Vol. 3, Form 73 – Personalized Evaluation of Fat Intake Self-Assessment Questionnaire (PEFI-Q) Instructions, Ver. 2*.

Printing the PEFI-F

When the PEFI-Q (ver. 2) is successfully scanned, it is automatically analyzed and the data necessary to generate the PEFI-F are stored in WHILMA. CCs will be able to print the PEFI-F to both locally (CC) and centrally (CCC scanned PEFI-Qs. Refer to information in *Vol. 2, Section 16.15.5.2 – Generating Tailored Feedback (PEFI-F)* and the PEFI 2003 Upgrade Notes.

6.16.3 WHILMA Resources for PEFI 2003

The section below describes the WHILMA resources available for PEFI 2003. This includes the *PEFI 2003 Mailing Selection Screen, PEFI 2003 Mailing Selection Report, PEFI 2003 Tracking Screen,* and the *PEFI 2003 Tracking Report*. Supporting information can be found in the PEFI 2003 Upgrade Notes.

6.16.3.1 PEFI 2003 Mailing Selection Screen

The *PEFI 2003 Mailing Selection Screen* includes all DM-I participants except participants who are: a) stopped DM intervention plus no mail follow-up status, b) absolutely no contact follow-up status, or c) deceased. During April through June 2003, nutritionists used the *PEFI 2003 Mailing Selection Screen* to designate: a) who will receive PEFI 2003, b) when (month) the PEFI-Q (ver. 2) will be mailed, and c) how the intervention will be delivered at each CC (i.e., centrally, locally, or not at all). Each CC was able to choose to do all participants centrally, all participants locally or a combination of central and local administration. All selections were made by July 1, 2003 when the *PEFI 2003 Mailing Selection Screen* was frozen in the WHILMA database. For information about the *PEFI 2003 Mailing Selection Screen*, refer to the PEFI 2003 Upgrade Notes.

6.16.3.2 PEFI 2003 Mailing Selection Report

The nutritionist uses the PEFI 2003 Mailing Selection Report to review the distribution of participants by mailing month and PEFI Administration (CCC, Local or None). The report can be sorted by nutritionist, group, or other parameters (e.g. undeliverable addresses). For further details about the report, refer to the PEFI 2003 Upgrade Notes.

6.16.3.3 PEFI 2003 Tracking Screen

The *PEFI 2003 Tracking Screen* allows the nutritionist to a) follow CCC and local implementation of PEFI 2003 and b) to enter optional data for local implementation. There are two tabs for the *PEFI Tracking Screen*: One for CCC administration and one for Local administration.

Central (CCC) Administration

The CCC tab of the *PEFI 2003 Tracking Screen* enables nutritionists to view participant progress in completing central administration of PEFI 2003. For each participant's PEFI-Q (ver. 2), the screen shows: dates PEFI-Q and PEFI-F labels were printed; date PEFI-Q was scanned, latest PEFI-Q event, reason PEFI-Q not mailed; and reason PEFI-F not mailed. This is read-only information, (i.e., staff cannot change data for central administration). The CCC will update the PEFI 2003 data weekly.

Local (CC) Administration

The Local tab of the *PEFI 2003 Tracking Screen* enables nutritionists to key-enter optional data for tracking local implementation. The optional data for PEFI-Q (ver. 2) include: date PEFI-Q provided, reason PEFI not

completed, and date PEFI-F provided. This is the same procedure used for the original PEFI intervention. Refer to *Vol. 2, Section 6.15.6.1 – PEFI Tracking Screen* for more information on how to enter optional data.

The Local tab also provides the PEFI-Q Form date and the Latest PEFI-Q event. The scanning process generates this information automatically. Nutrition staff do not need to data enter this information.

For more details about how to use the *PEFI 2003 Tracking Screen*, refer to the PEFI 2003 Upgrade Notes.

6.16.3.4 PEFI 2003 Tracking Report

The Lead Nutritionist (or designee) uses the *PEFI 2003 Tracking Report* to track implementation of PEFI 2003 for Central and Local administration. The report can be sorted by PEFI administration, nutritionist, group, and other parameters (e.g. latest PEFI-Q event, reason PEFI not completed).

Central (CCC) Administration

The *PEFI 2003 Tracking Report* provides the following information for each participant's PEFI-Q (ver. 2): PEFI-Q label date, reason PEFI-Q not mailed, PEFI-Q form date, latest PEFI-Q event, PEFI-F label date, reason PEFI-F not mailed.

Local (CC) Administration

The *PEFI 2003 Tracking Report* provides the following information for each participant's PEFI-Q (ver. 2): PEFI-Q form date, latest PEFI-Q event. Optional data (e.g. date PEFI-Q provided, reason PEFI not completed, and date PEFI-F provided) will only be displayed on the report if the CC enters the optional data on the *PEFI 2003 Tracking Screen.*

For further details about the *PEFI 2003 Tracking Report*, refer to the PEFI 2003 Upgrade Notes.

6.16.4 PEFI 2003 Intervention Summary

A summary of the completion rates for PEFI 2003 will be prepared after conclusion of the intervention. The summary will be modeled after the *PEFI Summary Report (PEFI 0003)* used for the original PEFI intervention. This report will show completion studywide and by CC. A preliminary report will be published from the February 2004 database and a final report will be published from the May 2004 database.

6.17 Closure of the DM Intervention Sessions

This section documents procedures for closure of the DM Intervention sessions.

6.17.1 Year 10 Sessions Overview

DM Intervention Year 10 began September 1, 2003 and ends August 31, 2004. Year 10 includes four sessions: Fall 2003 (10F), Winter 2003 (10W), Spring 2004 (10SP), and Summer 2004 (10SU). The overall theme for the final year of the DM Intervention sessions is *Protecting Your Investment*.

The overall goals for Year 10 are to: a) provide opportunities for participants to feel positive about the WHI and their contributions, b) promote participant dietary adherence through the WHI close-out visit, and c) prepare participants for closure of the DM Intervention sessions. Each Year 10 goal is addressed in every session – with more or less emphasis, depending on the particular session. The four sessions work together to accomplish the overall goals for Year 10. An overview of Year 10 is shown in *Figure 6.19 – Year 10 Sessions Overview*. Refer to *Volume 4 – Dietary Modification Intervention, Group Nutritionist Manual – Maintenance Sessions (Years 1998+)* and *Participant Manual – Maintenance Sessions (Years 5-9)* for the Nutritionist Guidelines and Participant Materials.

6.17.2 Final DM Intervention Session

Summer 2004 (10SU): Celebrating Your Investment in Women's Health is the final DM Intervention session. The overall goal of the session is to celebrate the WHI and acknowledge each woman's contribution. The 10SU session activities and materials are designed to provide a memorable and meaningful experience for participants. These materials and activities include:

- *"Celebrating Your Investment in Women's Health"* newsletter (also referred to as 'Dietary Change Fun Facts').
- Certificate of Completion (centrally developed, printed locally from WHILMA).
- WHI Dietary Change Session Summary (centrally developed, generated locally from WHILMA). [Optional]

The CCC will also provide special folders for these and other locally developed materials.

"Celebrating Your Investment in Women's Health" Newsletter

The *"Celebrating Your Investment in Women's Health"* newsletter and supporting session activity provide a way to thank participants for their extraordinary contributions to WHI and help them celebrate their participation in the DM Intervention sessions. Refer to *Volume 4 – Dietary Modification Intervention, Participant Manual – Maintenance Sessions (Years 5-9)* to see a sample of the "*Celebrating Your Investment in Women's Health"* newsletter.

Certificate of Completion

The Certificate of Completion acknowledges (and helps celebrate) that each participant has reached the end of the DM Intervention sessions. Refer to *Volume 4 – Dietary Modification Intervention, Participant Manual – Maintenance Sessions (Years 5-9)* to see a sample of the Certificate of Completion.

WHI Dietary Change Session Summary (Optional)

The WHI Dietary Change Session Summary recognizes each participant's contributions with a personalized summary of her DM Intervention session participation. Refer to *Volume 4 – Dietary Modification Intervention, Participant Manual – Maintenance Sessions (Years 5-9)* to see a sample of the WHI Dietary Change Session Summary.

6.17.3 Activities for Women Who Miss the Summer 2004 (10SU) Session

The 10SU session includes a make-up component divided into two parts (Part I and Part II). All participants who do not attend the 10SU session will receive the make-up Part I. As many of these participants as possible will also receive the make-up Part II.

Part I:

When a participant does not attend the 10SU session, send her the 10SU missed session packet. This packet includes:

- Cover Letter (Summer 2004 Group Session): centrally developed, CC-modifiable, printed locally from Public Folders.
- *"Celebrating Your Investment in Women's Health"* newsletter.
- Certificate of Completion.
- WHI Dietary Change Session Summary. [Optional]

The mailing and receipt of this packet is assumed; therefore, documentation is not tracked in WHILMA (i.e., no forms need to be completed and "make-up" is not documented).

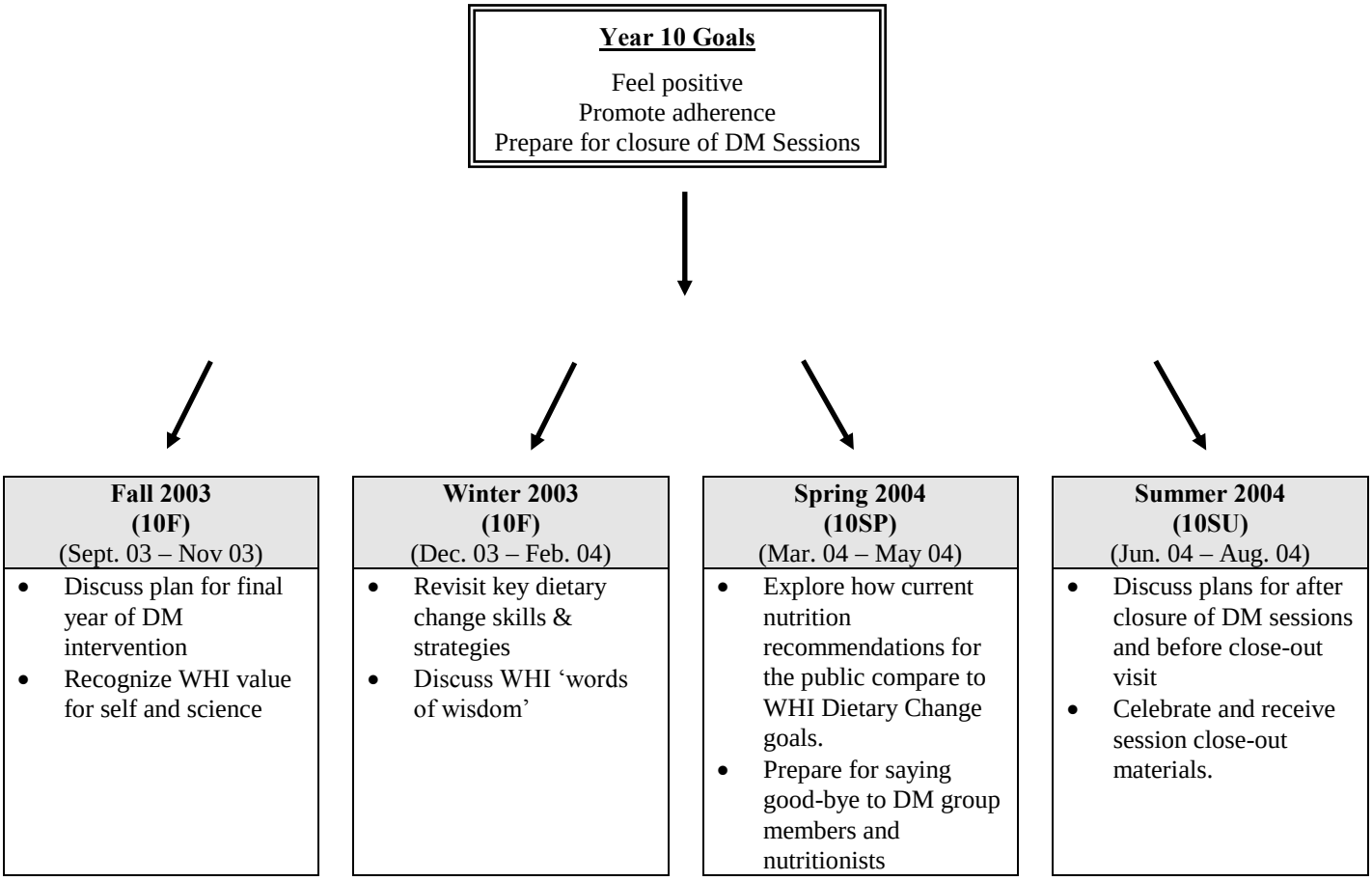
Part II:

After sending the 10SU missed session packet, contact the participant for an interactive discussion that includes a thank you for participating in the WHI Dietary Study and an opportunity to comment on her WHI experience (e.g., *What new things did you learn about your contributions to the WHI Dietary Study*? *What are your fondest memories about your participation in the WHI Dietary Study?*). Additional examples of questions to ask participants regarding their WHI experience are presented in the Nutritionist Guidelines for this session. The interactive discussion may take place in-person, by phone, or by mail (including e-mail) per the participant's needs and the staffing configuration at your CC. After completing the interactive discussion, document completion of the session in WHILMA using *Form 64 – Individual Data Sheet* (record '10SU' for *Qx. 5 – Purpose of Contact*).

Note: CCs who choose to do make-up by mail have the option to add the Make-up for Summer 2004 Group Session sheet to the 10SU missed session packet (printed locally from Public Folders). If the participant completes this sheet, document completion of the session in WHILMA using *Form 64 – Individual Data Sheet* (record '10SU' for *Qx. 5 – Purpose of Contact*).

All 10SU make-up activities, including data entry, are strongly encouraged to be completed by September 30, 2004.

Figure 6.19 – Year 10 Sessions Overview



Section 6
Dietary Modification (DM)

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SECTION 7

CALCIUM AND VITAMIN D INTERVENTION

INTRODUCTION

The objective of the Calcium and Vitamin D (CaD) component of the Clinical Trial (CT) is to determine the effect of supplementation with calcium and vitamin D primarily on the incidence of hip fractures and secondarily on the incidence of colorectal cancer, other types of fractures, other cancers, cardiovascular disease, and mortality. The addition of vitamin D to calcium supplementation is thought to enhance the effect of the calcium on the prevention of bone loss.

One year after randomization into the CT—Hormone Replacement Therapy (HRT) and/or Dietary Modification (DM)—eligible participants will be invited to join the CaD component. Participants have the option of taking one of two forms of CaD: chewable or swallowable. If they are interested in and eligible for CaD, participants will be randomized in a double-blind fashion into one of two arms:

- CaD intervention:

  1. **Chewable**:

     Chewable calcium carbonate 1000 mg elemental calcium per day, plus vitamin D3 400 IU per day (dispensed as two chewable tablets, each containing 500 mg of elemental calcium and 200 IU of vitamin D).

  2. **Swallowable**:

     Calcium carbonate 1000 mg elemental calcium per day, plus vitamin D_3 400 IU per day (dispensed as two **swallowable** pills, each containing 500 mg of elemental calcium and 200 IU of vitamin D). *Note:* dosage of Vitamin D changed from 125 IU to 200 IU in Spring 1998

- CaD placebo:

  A placebo calcium and vitamin D tablet that appears identical to the intervention tablet (dispensed as two chewable tablets or two swallowable pills of placebo)

It is estimated that approximately 45,000 women will be randomized to the CaD component (1,125 at each Clinical Center [CC]). Guidelines and requirements for implementation of the CaD component of the CT are included in this section. Each CC may devise policies and schedules for themselves within these recommendations and requirements to produce optimal performance in the Women's Health Initiative (WHI) CaD component and to provide appropriate care and follow-up of participants.

7.1 Recruitment and Randomization (Required)

Historically, if a participant was interested and eligible for the CaD component, she was invited to join the CaD component before her first annual visit (AV1) *or* she could be invited to join her second annual visit (AV2) if she had not been offered CaD at AV1. In March 1998, the Steering Committee approved offering the CaD component through AV2 for all participants (as well as between AV1 and AV2, at the clinic's option). Participants can be invited to join CaD at AV1 up to AV2, and randomized up to 2 months past the AV2 target date. Note that CCs are still required to offer CaD at AV1.

The procedures below describe the process for the AV1 or AV2, and can also be applied to any visit. For CaD randomizations between AV1 and AV2, the visit type must be marked according to the most recent routine contact (AV1 or SA2), not as a non-routine contact.

7.1.1 Preparation for the Annual Visit (Recommended)

Run a CaD eligibility determination on the participant from the WHILMA database before the target annual visit date. This eligibility determination will indicate if the participant is eligible for CaD based on medical history information received to date.

If the CaD eligibility determination returns a result other than "INEL" [WHILMA will not give an "eligible" result at this time], include in the pre-visit packet of materials (e.g., appointment reminder, *Form 33 - Medical History Update,* and *Personal Information Update - WHIP 0441*), the *Invitation to Join CaD* (see *Appendix F*) and your CC's CaD consent form. Mail this packet out to the participant at least two weeks before the appropriate annual visit. This CaD information should also be presented and reviewed with the participant at the annual visit.

The day before the annual visit, place two copies of your CC's CaD consent form, *Form 11 - Consent Status,* and *Form 16 - CaD Eligibility Assessment* in each eligible CT participant's annual visit file along with barcode labels with the participant's ID and name. The labels should NOT be applied to forms until the participant arrives for the visit. Additionally, labels should not be applied to medication bottles until randomization, when the WHILMA medication selection function is enacted.

7.1.2 Activities During the Annual Visit (Required)

CaD-related activities during the appropriate annual visit include:

- Determining the participant's interest in and eligibility for CaD.
- Providing her with complete information about the CaD component.
- Offering her a taste test of the chewable tablet, and/or a swallow test of the swallowable pill.
- Obtaining informed consent.
- Randomizing her to a CaD treatment arm.
- Selecting and dispensing a 6-month supply of CaD study pills.

Refer to *Volume 2, Section 16.3 - Annual (CT) and Third-Year (OS) Visit* for additional annual visit activities.

7.1.3 Eligibility (Required)

Participants who have been randomized and followed for at least one year in one or both of the other CT components (HRT and/or DM) are eligible for CaD. Participants enrolled in the Observational Study (OS) are **not** eligible for CaD. Participants interested in the CaD component must meet specific eligibility criteria before they can be randomized.

Eligibility criteria (and data sources) that must be met for CaD randomization include:

- Currently randomized to HRT and/or DM (WHILMA database).
- Willing to participate in CaD (*Forms 11* and *16*).
- Survivability of > 3 years (Clinical Practitioner (CP) judgment on *Form 16*).
- No history of hypercalcemia (*Form 16*).
- No history of renal calculi *(Form 16*).
- No kidney failure requiring dialysis (CP judgment on *Form 16*).
- No current daily oral use of corticosteroids (*Form 16*).
- No current use of calcitriol (*Form 16*).
- No dementia (CP judgment on *Form 16*).
- Vitamin D intake of less than or equal to 600 IU daily or willingness to decrease daily use to 600 IU or less (*Form 16*).
- Randomization up to two months past the AV2 target visit date.

Before *Form 16* is entered, the WHILMA eligibility determination for CaD is based on:

- *Form 30 – Medical History* (from screening).
- *Form 33 - Medical History Update* (from semi-annual visit).

If these data indicate no previous hypercalcemia or renal calculi (WHILMA result is not "INEL"), the participant is currently eligible for CaD and can be invited to the CC to further assess interest and eligibility.

7.1.4 CaD Information and Consent (Required)

The following procedures are required before the participant can be randomized.

7.1.4.1 CaD Study Pill Taste/Swallow Test Procedure

Overview

Clinical Centers are required to:

- Explain the option to take a chewable tablet or swallowable pill.
- Provide participants with a visual inspection of the CaD study pills.
- Offer a taste test and/or swallow test before CaD randomization.

It is recommended that these procedures be implemented during the informed consent discussion. Note that the participant can decline either test.

McKesson will supply separate bottles of CaD study pills for the taste and swallow tests, marked "CaD Taste Test" or "CaD Swallow Test." Neither the CC staff nor the participant will know if the tablet or pill being tested is the active or placebo study pill. Reorder additional "CaD Test" bottles from McKesson as needed.

Visual Inspection

When introducing the visual inspection of both formulations, emphasize the importance of the WHI CaD study for learning about whether the calcium and vitamin D can prevent broken bones and colon and rectal cancer. Stress the need for such scientific studies before prevention strategies can be recommended generally with

confidence. Tell the participant that you are going to show her a study pill similar to the one she would take as a participant in this part of the WHI. Drop a study pill from each bottle into their bottle caps for the participant to view (do not touch the study pills with your hands). Tell her the study pills are:

Chewable Tablet

- Meant to be chewed (but can also be crushed and swallowed with water or soft food).
- Peppermint-flavored.
- Similar to other chewable calcium tablets (like Tums®).

Swallowable Pill

- Meant to be swallowed with water.
- Similar to other swallowable pills .

Taste/Swallow Test

Tell the participant that the taste or consistency of the chewable tablet might seem a little different and encourage her to try one. If she refuses either or both tests, let her know this is optional but recommended. Recommend that she also try the swallowable pill. If she declines, throw the study pills used for visual inspection away in their respective study pill discard boxes.

If she agrees to the taste and/or swallow test, drop the appropriate pill from the bottle cap into her hand (again, not touching the tablet). As she tastes the chewable tablet, ask her to pay attention to its:

- taste
- consistency
- chewability

Give her a glass of water. As she tries the swallowable pill, ask her to pay attention to its:

- taste
- ease of swallowing

Evaluation and Follow-Up

Ask the participant if she has any questions about the study pills or the CaD study. Remind her that once she joins, no one can take her place. Refer to the *Questions and Answers: Calcium and Vitamin D Trial (for CC staff) (Appendix G - CC Reference Materials)* for answers to her questions.

Assess the participant's response to the visual inspection and the test of either or both formulations. CCs are encouraged to develop local strategies and guidelines for evaluation. Document on *Form 16 – CaD Eligibility Assessment* her formulation preference (chewable or swallowable). If the participant declines to participate in CaD, complete the staff impression item on *Form 16 - CaD Eligibility Assessment*. Be sure to let her know that her continued participation in the other clinical trial component(s) (i.e., HRT and/or DM) is important, very much appreciated, and will not be affected by declining participation in CaD. If the participant requests more time to decide, you may recontact her up to 2 months past the AV2 target visit date.

Document the participant's response to the visual inspection and the taste and/or swallow tests in the participant's contact notes. This information will help other staff who have future contact with the participant.

7.1.4.2 Informed Consent (Required)

Provide the participant with adequate information and time to give informed consent to CaD if she:

- Is currently eligible for the CaD component, according to the pre-visit eligibility determination.
- Has read the CaD consent mailed to her before or provided during the visit.
- Is interested in participating in CaD.

Begin an information-sharing session about the CaD component in a quiet, private area away from possible interruptions. During this session, review the CaD consent form with the participant and answer any questions she may have. A suggested script you might follow is contained in *Figure 7.1 – CaD Consent Script*. If you do not follow this script, however, you **must** cover the following points:

- The CaD study is completely voluntary and the participants may withdraw at any time. If she does chose to withdraw, no one else can take her place. Her decision will not affect her involvement in the other WHI component(s) to which she is randomized.

- Any information she gives will be held completely confidential and will be released to no one except WHI personnel and, if necessary, authorized Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) staff.

- Her response will be added to those of other women and only composite or grouped information will be released. Neither her name nor any other identifying information will be released in WHI reports or publications.

- The assignment to treatment groups is completely random, a computer makes the selection and both groups are equally important.

- **Study Pills:** The participant will be asked to take one CaD chewable tablet or swallowable pill two times a day (with meals). The pills will contain either active calcium and vitamin D or no supplements (placebo). The CaD study pills may be dispensed on an annual basis (if she has tolerated at least 6 months of the same formulation) or every 6 months. The participant may switch formulations at any time. After randomization is complete, the participant must limit her personal use of vitamin D to less than or equal to 1,000 IU.

- **Schedule:** The participant will be monitored at the same schedule as her other WHI component(s), with the exception that she will be interviewed every six months to discuss any symptoms or health events to be sure that taking pills is still safe for her.

- **Risks:** Some participants may notice short-term gastrointestinal side effects (constipation, bloating, or gas). There is a very small risk of more serious problems such as high blood calcium or kidney or bladder stones.

The CaD consent form must be signed and dated after the appropriate CC staff person reviews the content in detail with the participant, she had had the chance to ask questions, and she agrees to participate. The appropriate WHI signer should be determined by your PI and approved by your local Institutional Review Board (IRB) (some IRBs may require a specific signer and/or witness). You must give the participant one copy of the consent form to take home with her and place a signed copy of the consent form in her file.

Some participants may want to go home and discuss this decision with others before agreeing to participate. Provide these participants with a stamped, addressed mailing envelope and two copies of the consent form (so they can mail in a signed copy and keep the other) or plan to copy the signed consent form after it's returned and mail it back to the participant. Your local Institutional Review Board (IRB) may have specific guidelines for consent by mail. Note that the participant should **not** be randomized to CaD and CaD study pills should **not** be dispensed until the signed consent is received.

After a thorough informed consent discussion and adequate opportunity to consult with others, document the participant's decision on *Form 16 - CaD Eligibility Assessment*. If the participant is interested in joining CaD, obtain her signature on the CaD consent form, obtain additional signatures as required by your IRB, provide her with a copy of the consent, and complete *Form 11 - Consent Status*. If she is not willing to participate, record this information on *Form 16 - CaD Eligibility Assessment* and continue to follow her for the other clinical trial components in which she is participating.

7.1.5 Randomization Activities (Required)

The final eligibility determination for and randomization to CaD is a WHILMA database function that requires data entry of *Form 11 - Consent Status* (with contact date of less than 6 months) and *Form 16 - CaD Eligibility Assessment* (with contact date of less than 1 month).

To randomize a participant to CaD, enact the WHILMA randomization function and record appropriate information on *Form 8 - Randomization/Enrollment Log*. Randomization to CaD occurs at a ratio of 50:50, active treatment:placebo.

7.1.6 Implementing the CaD Intervention After Randomization

The CaD intervention consists of the study pills, the *CaD Handbook* (see *Appendix F.3.15*), and discussions with participants on the specifics of the intervention. Use the four steps below and the information sheet when initially providing the study pills to each participant after randomization. Review them, as necessary, at subsequent contacts.

Step 1 - Introducing the CaD Intervention to the Participant (Required)

Providing the CaD Handbook

Welcome the participant to the CaD and congratulate her on her participation so far. Hand her a copy of the *CaD Handbook*. Explain that this handbook contains the basic information she will need and that you and she will cover some of it right now. Tell her that if she ever has any questions she should ask them as you go along so that she will not forget them.

Reviewing the Importance of the CaD

Review the importance of the CaD to women's health and to the field of prevention science. Remind the participant of her importance to the study and of her generosity in volunteering her time and effort. Discuss the scientific outcomes of the study (e.g., effects of CaD on bone fractures and colorectal cancer). Also reassure the participant by emphasizing the safety points in the CaD. Use the *Questions and Answers: Calcium and Vitamin D Trial (for CC staff*) (in *Appendix G*) to help guide your responses.

Step 2 - Taking the CaD Study Pills

CaD study pills are bottled as 215 pills per bottle for the chewable or 430 pills per bottle for the swallowable formulations. Dispense one or two bottles (depending on the formulation) at randomization to cover the first six months, according to the procedures outlined in *Section 15.4.5 - Dispensing CaD Study Pills.* Clinical Centers should dispense only a 6-month supply of either formulation until the participant has been tolerant and adherent of the **same** formulation for at least one year.

Instructions for Taking Pills (Required)

Describe the label contents to the participant. Offer her a non-child resistant cap. (See *Section 15.1.3. - Child-Resistant Caps*.) Review with the participant the *CaD Handbook* (given above), telling her:

- To take one study pill two times each day with meals (e.g., one with breakfast and one with dinner).
- To chew the tablet or swallow the pill (show the participant how to do this). The chewable tablet may be broken into small pieces to swallow with water.
- To contact the CC if she is having any problems taking the study pills. The CC staff can provide options that may make it easier to take the study pills.
- That she may have minor symptoms (e.g., constipation, bloating), what she can do about them, and what symptoms warrant contacting a health care provider (i.e., flank pain or bloody urine).

It is recommended that you caution the participant not to shake the bottle of CaD chewable tablets excessively because the pills easily crumble. If the participant's randomization to CaD occurs after she has left the CC (but within the 2-month window around the target visit date), CaD study pills can be selected, dispensed, and sent to her through the mail. Along with the study pills, mail out the *CaD Handbook* and confirm by telephone that she understands the instructions. If the participant wants a non-child resistant cap, she must sign the appropriate consent form.

Using the Pill Organizer (Recommended)

Give the participant one or two seven-day pill organizers (if needed) and show her how to use it as a reminder to take her pills. Discuss using it also for other medications she may take. Let her know that she can have **two** pill organizers (one for the morning, one for the evening) to help her remember both pills each day (this may be particularly useful if she also takes other medications).

Designing a Reminder System (Recommended)

Ask the participant how she is going to remember to take the pill every day. Ask her about other pills or daily activities she has and how she remembers to do these things. Help her to integrate the CaD study pill with other daily pills or activities. If she (or you) seems concerned with her ability to remember, or she indicates that she has had trouble in the past remembering to take pills or perform other daily activities, help her to design a cueing or reminder system to help her remember. Explain what a cue is (a cue is anything that will remind the participant to take her pill every day—e.g., pill organizers, post-it notes on refrigerators or mirrors). Consider time of day, placement of cue or reminder, ease of seeing the cue, and consistency of the cue, when designing the reminder system. Ask the participant how she will remember to take her study pills when she is in an unusual situation (e.g., on vacation, traveling, or weekends).

Identifying and Building Skills (Recommended)

Ask the participant if she thinks she will be comfortable performing the activities needed to participate in the CaD intervention. Discuss those activities that she expresses concern about. Ask her to rehearse interactions or activities with you about which she is uncertain. Recommend specific behavioral goals and identify steps to achieve the goals. For example, remembering to take pills daily could include cueing the participant for a specific time and place to take the pill, having a supply of pills to take at that time and place, and being assertive in order to take the pill in the presence of others. Ask her to try out the new behaviors and let you know how they work at the next contact.

Review (Recommended)

Review the steps involved in taking CaD study pills with the participant. Ask the participant questions that allow you to be sure she understands all the information and is ready to participate. An example of such questions includes, "How are you going to remember to take your pills?" Remind her to call with any questions.

<u>Step 3 - Understanding Symptoms</u> (Recommended)

Identify Fears and Beliefs

Ask the participant what she is feeling about starting on the pills. Identify any fears, worries, or apprehensions that she may have about taking study pills. Ask her if she, her friends, or family members have had negative experiences with taking calcium or vitamin supplements. Ask her what she expects to happen to her and what the consequences of these events will be. Listen and acknowledge the participant's beliefs about CaD and correct any misperceptions she may have.

Reviewing Possible Symptoms

Discuss with the participant possible symptoms that she may experience. Indicate that each woman is different and that her experience may be the same or different from other women. Discuss her trial experience to date. Emphasize the long-term nature of the program, including long-term gains. Discuss with her the ways that the trial procedures promote participant safety and remind her that if she has any questions or problems she should call the CC right away.

Review

Review the issues she brought up about her previous experiences and beliefs about CaD. Also, identify any issues about which you have more up-to-date information to allay any fears and concerns in the future.

Step 4 - Discussion of Routine Monitoring (Recommended)

Reasons for Monitoring

Explain to the participant the reasons for monitoring (i.e., ensuring the safety of the participant and collecting follow-up data).

Monitoring Activities

Review the basic schedule of follow-up and monitoring that occurs as part of the CaD. Ask the participant questions to determine if she understands her responsibilities and activities in the trial and the reasons for them. Ask her if she has any other questions at this time.

7.1.7 Exit Interviews (Recommended)

Review the visit activities with the participant to be sure you completed all the necessary tasks, built rapport, and fostered a commitment to the study.

Be sure that the newly randomized participant has appropriate CaD materials to take home (in addition to those for the other CT components) including:

- Clinical Center-specific CaD consent form (required).
- *CaD Handbook* (required; see in *Appendix F.3.15*).
- A 6-month supply of CaD study pills.
- One to two WHI pill organizers (if needed; can be ordered annually with quarter 3 orders on *Form 172 - Supplies Order*).
- CaD chart labels (optional; can be ordered quarterly on *Form 172* and given to participant or sent to her primary care provider).
- Confirmation of randomization (optional).

Inform the participant about what to expect at the next 4-week contact and answer any questions she may have. Remind her to contact the CC any time she has questions or concerns.

7.2 Follow-Up Contacts with CaD Participants

After CaD randomization, a phone contact at four weeks (with a target window of ± two weeks on either side) is required (see *Section 16.1 - Early Adherence & Safety Contact*). Otherwise, CaD follow-up, as with the other CT components, occurs every 6 months. Follow-up procedures for CaD participants are essentially the same as those required by the participant's initial trial component (HRT and/or DM) with semi-annual contacts (phone, mail, or visit as appropriate and determined by CC) and annual visits. Note that a CaD participant should only be dispensed a 6-month supply of CaD study pills until she has tolerated the same formulation for an entire year.

Before each semi-annual contact and annual visit, remind all CaD participants to bring in (or mail in, as appropriate) their CaD study pills, including those in their bottles and pill organizers.

7.2.1 Forms Review (Required)

Complete *Form 17 - CaD Management and Safety Interview* and review at each semi-annual and/or annual contact for any new-onset renal calculi, hypercalcemia, vitamin D or calcitriol use that would necessitate permanently discontinuing her CaD study pills (see *Section 7.3 - Adverse Effects*). Note the participant may opt to change study pill formulation at this time.

Review her *Current Supplements (Task 45*), if appropriate, to confirm she is not taking more than 1,000 IU of vitamin D daily. If she is taking > 1,000 IU daily and is unwilling to decrease her dose, discontinue her CaD study pills. They may be restarted if she decreases her dose of vitamin D (to ≤ 1,000 IU) in the future.

Complete *Form 54 - Change of Medications* if you temporarily change or discontinue her CaD study pills or *Form 7 - Participation Status* if she changes intervention status permanently.

7.2.2 Identifying Problems at Participant Contacts

Use every contact with a participant to identify issues or problems with pill-taking, symptoms or safety, adherence, and retention. Review *Section* 17.2.3 - *Reasons for Poor Retention and/or Adherence* to identify potential reasons that participants would stop or decrease pill taking. Use the steps below to identify adherence problems.

<u>Step 1 – Adherence Collection</u> (Required)

At each semi-annual contact and/or annual visit, as appropriate, weigh the participant's returned CaD bottles or have the participant provide an estimated count. Refer to *Section 15.6.2 - Adherence Assessment* for pill weighing and pill estimation procedures and appropriate troubleshooting.

<u>Step 2 - Monitoring Adherence and Symptoms</u> (Recommended)

Adherence is defined as taking CaD study pills at 80% of the appropriate amount or higher. WHILMA will estimate this at follow-up using the participant's bottle weight.

7.2.2.1 Switch of Formulations

At each contact with a participant, evaluate the potential benefit of switching formulations. Refer to *Figure 7.2 – New CaD Formulation Scripts* for suggested scripts to use when a participant is asked to consider switching formulations.

7.2.2.2 Intensive Adherence Plan (Required)

Refer women who have adherence assessed at < 80%, or seem at risk for low adherence, to the appropriate Intensive Adherence Plan (IAP) coordinator. See *Section 17.2.2.2 – Initiating Special Activities for HRT and CaD Retention Challenges [IAP]*).

7.2.3 Dispense Study Pills (Required)

Select and dispense to the participant another 6- to 12-month supply of CaD study pills. Provide the participant with another *CaD Handbook* and pill organizer, if needed. If she has been having trouble with remembering the study pills or taking them twice a day, offer her the option of taking two pills once a day (see *Table 7.1 - Step-Down Procedures for Managing Adherence Problems or Minor Adverse Effects).*

7.2.4 Osteoporosis Handout

CCs are not required to give the *WHI Update – What You Should Know About Osteoporosis* and guidelines to participants. However, if CCs decide to give participants information on osteoporosis, they must use this handout. (See *Appendix F – Required CC Printed Materials, Figure F.3.11*.)

Table 7.1

Step-Down Procedures for Managing Adherence Problems or Minor Adverse Effects*

Participant Problem	**Initial Option to Offer**	**Other Options if Problem Doesn't Resolve (prioritized)**
Taking study pills with food (difficulty remembering or having food available)	Try taking study pills without food and re-evaluate for possible minor adverse effects (see below)	N/A
Remembering to take pills twice a day (even using the WHI pill organizer)	Take two pills once a day for one to three months and re-evaluate.	N/A
Taking the specific study pills (e.g., too big, don't like the taste, can't swallow)	Change to the other formulation and re-evaluate	Crush/break/cut the chewable tablet. Mix the pieces up with liquid or soft foods and/or simply chew or swallow the pieces, as tolerated. Cut the swallowable tablet (provide her with information about pill cutters) and swallow the pieces individually. Take two pills once a day for one to three months and re-evaluate. You may need to step down further to one pill once a day, if necessary to retain the participant).
Experiencing GI symptoms or other minor adverse effects	Take only one pill once a day for one to three months and re-evaluate	Take only one pill every other day (or every two to three days) for one month and re-evaluate. Stop taking pills for one month and re-evaluate

*Note that you should continue to re-evaluate these problems and options (at routine or non-routine contacts) and, if possible, bring the participant back up to the study regimen (one study pill twice a day).

7.3 Adverse Effects

Trial participants may experience adverse effects ranging from mild inconvenience to more serious conditions. Take time to identify potential adverse experiences early so that appropriate and prompt treatment, referral, and study medication stoppage decisions can be made. Participants are informed about possible major and minor effects of calcium and vitamin D before randomization (when informed consent is obtained) and after randomization (each time study pills are dispensed). The *CaD Handbook* also reviews these adverse effects. (See *Vol. 2, Appendix F*.)

7.3.1 Monitoring for Adverse Effects (Required)

Information about CaD adverse effects may be collected from:

- *Form 17 - CaD Management and Safety Interview.*
- *Form 33 - Medical History Update* or *Form 33D - Medical History Update (Detail)*
- Participant calls to the CC between visits.
- Reports of symptoms to CC staff during scheduled or unscheduled contacts.

Adverse effects that are life-threatening and previously unassociated with CaD constitute serious adverse effects (SAEs) and must be reported to the Program Office and the Clinical Coordinating Center (CCC). See *Section 15.7.2.2 - Reporting SAEs.*

7.3.2 Minor Adverse Effects (Required)

Few minor adverse effects are anticipated with the CaD component. Minor adverse effects that have been reported in the past have usually been gastrointestinal (GI) in origin. Not all women will have such symptoms, and the severity and frequency of symptoms will vary among women, as will their responsiveness to symptom management or dosage changes. These symptoms are often noted with any medications or placebo pills. Therefore, remind the participant that these changes may not be due to the study pills. When the participant starts on CaD study pills, inform her of the possible minor adverse effects that could occur as listed on the *CaD Handbook.*

Tell her that these symptoms are in most cases not harmful, but that she should contact the CC if any of the symptoms become severe or very uncomfortable. Reassure her that most minor symptoms associated with CaD study pill use resolve spontaneously and within 2-3 months.

7.3.2.1 Management of Minor Symptoms

Management of minor adverse effects of CaD is primarily palliative or symptom-related. If the participant reports GI symptoms, reassure her that these symptoms may not be due to the study pills and that serious side effects of CaD therapy are rare. Remind her to take her study pills with meals if she is experiencing minor adverse effects. Review the *CaD Handbook* with the participant and recommend that she also try other simple strategies for managing these minor symptoms at home, such as increasing fluid intake. Also refer to *Questions and Answers: Calcium and Vitamin D Trial (for CC staff*) (*Appendix G.1.1*) for guidance with your responses. Encourage her to call the CC if she has any questions or problems.

If symptoms are intolerable or severe enough that participant adherence/retention is a threat, step-down her dose to one study pill per day (or one study pill every other day or every one to two days, as tolerated) with meals for one to three months. See *Table 7.1 – Step-Down Procedures for Managing Adherence Problems or Minor Adverse Effects.* After this time period, try to gradually increase her dose back up to two study pills per day. If she cannot tolerate two study pills per day, she may need to continue at a lower dose for a longer period of time or the duration of the study. If symptoms persist on the lower dosage, encourage her to see her

primary care provider to rule out other causes. Document any study pill dosage changes on *Form 54 - Change of Medications*.

7.3.3 Major Adverse Effects and Events (Required)

Major adverse effects of CaD are expected to be very rare, but may include the development of:

- Renal calculi (kidney stones), or
- Hypercalcemia (increase calcium levels in the blood)

7.3.3.1 Management of Major Health Effects and Events

If a CaD participant reports the following on *Form 17 - CaD Management and Safety Interview* and/or *Form 33 - Medical History Update (Detail)*, permanently discontinue her study pills and record this action on *Form 7 - Participation Status*:

- The development of renal calculi
- The development of hypercalcemia
- Kidney failure requiring dialysis requires a participant to permanently stop taking her CaD study pills. Dialysis raises a safety concern because Vitamin D absorption is likely to be compromised in renal failure participants.
- She is taking calcitriol (e.g., Rocaltrol, Calcijex) (until she discontinues it)
- She is taking > 1,000 IU Vitamin D in personal use (until she is taking < 1,000 IU)

Other major health events may result in the temporary discontinuation of CaD study pills, including:

- Any hospitalization
- Diagnosis of osteoporosis
- Myocardial infarction
- Accidents resulting in immobilization
- Stroke
- **Or** any severe illness in which the administration of calcium/vitamin D is temporarily inappropriate

The decision to temporarily stop CaD study pills is made by a CC PI, physician-designee, or the participant's health care provider. Although taking CaD in the situations above is not likely to be contraindicated, the attending physician may wish to temporarily suspend all medications while a participant is under treatment and administer only medications specific to the condition being treated. Report all decisions to temporarily stop study pills on *Form 54 - Change of Medication*. Complete a second *Form 54* when study pills are resumed. Complete a *Form 7 - Participant Status* if study pills are stopped for more than 3 months.

7.3.4 Unblinding (Required)

The CaD component is a double-blind trial; all CC personnel and CaD participants are blinded to a participant's treatment arm. In addition, all Bone Density site CC staff, other than the person doing the bone densitometry, should be blinded to any loss or gain in bone mineral density.

In some instances of serious adverse effects, the primary care provider may want the participant to be unblinded. If the CC PI or physician-designee decides that unblinding is necessary, the CC Unblinding Officer

will execute the WHILMA database unblinding function, which will require input of data regarding rationale for unblinding. (See *Vol. 5 - Data System, Section 6.5 - Unblinding Procedures*.) WHILMA will provide the treatment assignment and automatically log the unblinding event in the database.

The Unblinding Officer will provide the treatment assignment information only to the CC PI, physician-designee, or primary care provider, as appropriate. Outcomes ascertainment bias can be minimized by maintaining participant blinding, even when unblinding of some personnel becomes necessary. Document in the participant's file that unblinding has occurred, but do not record the treatment assignment in the participant's file.

Figure 7.1
CaD Consent Script

Suggested Script for CaD Consent:

"There are several points I would like to go over with you about the Calcium and Vitamin D trial. I'm sure you have several questions about this part of the study, and this information may answer some of these questions.

As with all parts of the Women's Health Initiative, taking part in the Calcium and Vitamin D trial is completely voluntary and you may drop out at any time. You may choose to answer or not to answer any questions on the study forms. Any information that you give is kept confidential and will only be seen by WHI staff and, if necessary, the Food and Drug Administration (FDA). All of your answers are grouped with the answers of other women in the study, and only this grouped information is released. Neither your name nor any other type of identifying information will be released in any reports.

You can join the Calcium and Vitamin D trial if you don't have health problems that might make taking the pills unsafe for you. Women who join the Calcium and Vitamin D trial will be placed by chance in either a 'Comparison' group or a 'Calcium and Vitamin D' group. A computer makes the selection for the groups so that it is fair. No one knows beforehand who will be in each group or has anything to do with what group you will get. Before you sign up, you must be willing to take part in either group. Both are equally important because everything we learn will come from comparing the groups. Once you begin, no one can take your place in the study group to which you've been assigned.

Women in both groups will be taking study pills. If you're in the Comparison group, you'll be taking pills that don't contain any supplements. If you're in the Calcium and Vitamin D group, you'll be taking pills that contain Calcium and Vitamin D.

You will be placed by computer into one of the groups and neither you nor the Clinic staff will know to which group you have been assigned. However, if there is some kind of medical emergency we can, if necessary, quickly find out which group you're in and give this information to your doctor.

When you join, you'll be asked to take a study pill twice a day with meals. You will be given a choice between two types of study pills, one you can chew and the other you can swallow.

Regardless of which group you're placed in, you may make follow-up visits to the Clinical Center as often as every six months to see how you're doing and to give you more study pills. Calcium and Vitamin D activities during these visits will take about 15-30 minutes.

Your participation in the other WHI clinical trial components will not change regardless of your decision about the Calcium and Vitamin D trial. Participation in the Calcium and Vitamin D trial will not involve any additional tests or procedures.

Occasionally, women who take Calcium and Vitamin D may experience symptoms or side effects. These symptoms may include constipation, heartburn, upset stomach, gas, or bloating. Not all of you will have these symptoms and for those who do, they may be somewhat different for each woman. Most of the time these symptoms are mild and not harmful, but you should contact the Clinical Center if any of the symptoms become severe or too uncomfortable.

Very rarely, serious problems like kidney stones or high calcium in the blood could happen. If so, the Clinical Center staff will stop your study pills so that these problems won't get worse. The health care professionals here are very concerned for your safety and will check regularly for the development of these problems.

Remember, you can call the Clinical Center at any time if you're having any problems or if you have any questions. Do you have questions at this time?"

Figure 7.2

Swallowable CaD Scripts for Participants Randomized to CaD

A. CaD ADHERENCE SCRIPT (for participants who have dropped):

There has been an exciting new change in the Calcium and Vitamin D program! Other women in the Calcium and Vitamin D program, like you, have stopped taking their pills, because they really did not like the taste or texture of the chewable tablet. Now the study pills come in a pill form you can swallow. These new pills can be taken with water, like any other pill. You would still take one of these pills twice a day with meals, and you would still get either the active or inactive (placebo) form, just like when you took the chewable tablets.

We invite you to think about trying this new pill and continue to be a part of the Calcium and Vitamin D program. This is a very important study that will give us many answers to questions about osteoporosis, broken bones, and cancer. We do appreciate your continued efforts in this very important study and for being a part of the answer in WHI.

B. CaD UPDATE SCRIPT (for participants with problems with the chewable formulation):

There has been an exciting new change in the Calcium and Vitamin D program! Now the study pill comes in a pill form you can swallow. These new pills can be taken with water, just like any other pill. You would still take one of these pills twice a day with meals, and you would still get either the active or inactive form, just like when you took the chewable tablets.

If you do not have a problem now taking the tablet that you chew, you probably should continue with that. However, if you are having a problem, you should consider switching to the pill you swallow. If you do choose to switch to the new pill, we want you to know that you can always switch back to the other tablet at your next visit.

The Calcium and Vitamin D study will give us many answers to questions about osteoporosis, broken bones, and cancer. We do appreciate your continued efforts in this very important study and for being a part of the answer in WHI.

C. SWALLOWABLE CaD INTEREST SCRIPT (for participants interested in the new swallowable CaD):

These new study pills were developed because some women did not like the chewable form. Let me show you the new study pill that can be swallowed (*drops a swallowable pill from "test" bottle into the bottle cap*). Would you like to try taking it now?

If yes, drop the pill from the bottle cap into the participant's hand and give her a small cup of water and continue with script. If no, just continue with script:

You would just take one of these pills twice a day with food. Remember, you were assigned to either an active or inactive pill when you joined the CaD program. This new pill comes in both an active and inactive pill form—neither you nor the WHI staff know which form you're taking.

If she chooses to take the new pill form, dispense a six-month supply only. Do not dispense more than a six-month supply until the participant has tolerated at least a full-year's worth of one of the formulations.

Section 7
Calcium and Vitamin D Intervention

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SECTION 8

OBSERVATIONAL STUDY

INTRODUCTION

A wide variety of important clinical and public health issues will be assessed with the Observational Study (OS). The most important purpose is the testing of new hypotheses with regard to risk of cancer, cardiovascular disease (heart disease and stroke), fractures and other major illnesses in post menopausal women. This will be achieved by relating information obtained on baseline characteristics to subsequent illness events and mortality. In addition, the gathering of biological specimens at baseline for storage and later analysis will allow etiologic hypotheses involving biomarkers to be examined in nested case-control or case-cohort studies.

The large size of the overall cohort (100,000), combined with the effort that is to be made to include sizable proportions of members of racial minorities, will permit the identification of risk factors for a number of the more common health outcomes in individual minority groups. Minority women have not been well represented in most past or present cohort studies of cardiovascular disease, cancer, or fractures. The OS can be expected to enroll almost 20,000 minority women as subjects. With these much greater numbers, it can begin to explore interracial differences in risk factors for conditions that occur with relatively high frequency, e.g., the major cancers, cardiovascular disease, and hip or forearm fractures.

Women who are interested in participating in the Women's Health Initiative (WHI) and who satisfy the OS eligibility criteria but who are not interested or eligible for the Clinical Trials (CTs) may be invited to participate in the OS. The OS has no intervention arm. Women may enter the OS during or between any of the three screening visits, although the majority are expected to enter at Screening Visit 1 (SV1).

Data on the OS participants will be obtained from questions they answer and from physical examinations and laboratory tests. Women in the OS will complete the same baseline questionnaires as the CT participants. Women in the OS will also complete a supplemental OS questionnaire at the time of enrollment. The supplemental questionnaire will obtain additional information about exposures and risk factors relating to the epidemiology of primary outcomes of the OS.

OS participants will be followed-up by means of annual self-administered mailed questionnaires. These questionnaires will ascertain updated information on hospitalization(s) and the occurrence of other outcomes of interest since the previous medical history update, changes in a few key exposure variables, and updated personal information (change in address, etc.).

At three years, all OS participants will complete a Clinical Center (CC) visit in addition to the follow-up questionnaires. The three-year visit will include physical measures and questionnaires.

8.1 Eligibility for the OS

Eligibility criteria for the OS are similar to the CT. However, some women who do not fulfill all the eligibility requirements for one or more arms of the CT will be eligible for the OS. Inclusion criteria for the OS include the following (see *Vol. 1 - Study Protocol and Policies, Section 1 - Protocol, Section 4.4 - Study Population* for eligibility and exclusion criteria):

- Female volunteers of all races and ethnicity, with or without a uterus or ovaries.
- Aged 50-79, inclusive, at the screening contact (*Form 2/3 - Eligibility Screen*).
- Postmenopausal, based on the Dietary Modification (DM) menopausal algorithm (see *Section 4.5.2 - Definition of Postmenopausal Status*).
- Likely to be residing in the study area for at least three years after study enrollment.
- Providing written informed consent.

Women who are ineligible for the OS are also ineligible for the entire WHI study. The following **exclusion criteria** apply to the OS (as well as the CT):

- Any medical condition associated with predicted survival of less than three years in the judgment of the CC physician (e.g., class IV congestive heart failure, obstructive lung disease requiring long-term ventilation or supplemental oxygen in the past, severe chronic liver disease with jaundice or ascites, kidney failure requiring dialysis, sickle cell anemia).
- Alcoholism.
- Other drug dependency.
- Mental illness, including severe depression.
- Dementia.
- Active participant in any other intervention trial where participants are individually randomized to an intervention or control group.

See *Vol. 5 - Data System, Appendix C.2 - Eligibility Criteria* for how each criterion is mapped to data on the questionnaires.

8.2 Inviting Women into the OS

8.2.1 Identifying OS Participants

Women who satisfy the eligibility criteria listed in *Section 8.1 - Eligibility for the OS,* may be enrolled in the OS. OS participants will be recruited from four sources:

1. All women who are found to be ineligible for the CT during the screening visits (SV1-SV3), but who satisfy the eligibility criteria for the OS, should be invited to enter the OS. This includes women who become ineligible between visits. When it becomes clear that the woman is ineligible for the CT, do not continue any procedures required by the CT. Enter all data collected up until this time, however, so that the reason for ineligibility is recorded in the database.

2. All women who are eligible for the CT (and hence also eligible for the OS) but who become uninterested in participating in either the Hormone Replacement Therapy (HRT) or the DM components of the CT during the screening visits (SV1-SV3) should be invited to enter OS. This includes women who become uninterested in the CT between visits. Do not continue CT procedures, but enter all data collected up until the time she became uninterested in the CT.

3. Some women who, during the screening process before SV1, are found to be eligible for the OS, but who are ineligible or uninterested in the CT, should be invited to participate in the OS. The number of such women invited into OS should be a sufficient number to meet the CC's enrollment target. These women should be scheduled for SV1.

4. Because of the approximately one year time lapse between the start of the CT and the start of the OS, Vanguard Clinical Centers (VCCs) may already have screened women who are either ineligible for the CT or unwilling to participate, but who are eligible and willing to participate in the OS. Vanguard Clinical Centers should review their screening records to identify potential OS participants falling into these categories. Potential OS participants identified from screening records may be recontacted and invited to participate in the OS.

8.2.2 Determining Eligibility for the OS

To determine eligibility for the OS, a woman must have completed *Form 2/3 - Eligibility Screen* and CC staff completed *Form 6 - Final Eligibility Assessment*. An eligibility determination for a woman can be made in WHILMA at anytime, and if appropriate, the woman may be invited into the OS if the minimum eligibility criteria are satisfied (age-eligible, post-menopausal, likely to reside in the area for three years and no exclusionary conditions).

8.2.3 Informed Consent for OS

Once a potential OS participant has been identified and has been found to meet the eligibility requirements outlined in *Section 8.1 - Eligibility for the OS,* she should be invited to participate in the OS. All OS participants are required to sign the OS Consent Form as part of the enrollment process. In addition, the Initial Consent Form should have been completed or should be completed at the beginning of SV1 (see *Section 4.2.4 - Guidelines of Activities*).

For women who enter the OS while at a CC visit, describe the nature of the study to her (see *Section 4.2.5.1 - OS Informed Consent* for suggested script). Give her a copy of the OS Consent Form and let her read it and ask any questions she has. Ask her to sign the OS Consent Form and give her a copy of the OS Consent Form for her records (see *Section 4.2.4.3 - Initial (Screening) Informed Consent* for a more detailed description of the OS informed consent procedures). *Form 11 - Consent Status* should be completed and data entered by CC staff when the consent form is signed or the participant refuses, to indicate the participant's consent status for eligibility and tracking purposes.

Clinical Centers may develop a consent form that combines all the elements of the Initial Consent Form and the OS Consent Form for women who come to SV1 specifically to enter the OS. (All changes to consent forms including the combining of Initial Consent with OS Consent require approval from the Project Office.) If a combined consent form is used, indicate on *Form 11 - Consent Status* that both Initial Consent and OS Consent have been obtained.

8.2.4 Entry Into OS Outside a CC Visit

Some women may become uninterested or ineligible for CT between SV1 and SV2 or between SV2 and SV3. For women who have completed the OS tasks outlined under *Section 8.3.1 - Questionnaires and Procedures Administered at a CC Visit* but become eligible for the OS between CC visits, entry into OS may occur outside a CC visit (CC option). Clinical Centers should develop procedures for mailed consent that are approved by their Institutional Review Board. The recommended procedure is to invite the woman to enroll in the OS by telephone (see *Figure 8.1* for sample telephone script) and then to mail her a packet containing: a cover letter, the "Welcome to the OS" handout, two consent forms (signed by the appropriate WHI CC signee), the self-administered questionnaires that she has not yet completed, the WHI magnet, optional health education materials (e.g., Breast Self-Exam [BSE] shower card, health pamphlets) and a self-addressed, stamped, return envelope. The cover letter should ask her to sign both consent forms, return the one with the questionnaires, and keep the other for her records. A sample cover letter is included in *Appendix E.6.1*.

The CCs should take into consideration each woman's language and reading ability in deciding whether or not the option of enrollment into OS outside a CC visit is appropriate.

8.3 Baseline Procedures for OS Participants

A woman must have completed all the required OS tasks to be enrolled into the OS. See *Vol. 5 - Data System, Appendix C.1 - List of Tasks Required for Randomization*.

All following questionnaires must be completed to determine eligibility:

Form 2/3 - Eligibility Screen

Form 6 - Final Eligibility Assessment

8.3.1 Questionnaires and Procedures Administered at a CC Visit

Certain tasks, outlined in this section, must be completed during a CC visit. If these tasks have not already been completed, they should be administered. If they cannot be completed during the visit at which a participant enrolls in the OS, she should be given a CC appointment to enable the completion of the outstanding CC visit tasks.

The procedures for the required OS CC tasks are identical to those for the CT, except for one change to blood draw procedures (see below).

The following questionnaires administered by CC staff during a CC visit are required on all OS participants:

Initial Consent (and *Form 11 - Consent Status* indicating Initial Consent has been signed.)

OS Consent (and *Form 11 - Consent Status* indicating Initial Consent has been signed.)

Form 43 - Hormone Use

Current Medications (direct data entry or *Form 44*)

Current Supplements (direct data entry or *Form 45*)

The following CC procedures are required on all OS participants:

Form 80 - Physical Measurements

Form 100 - Blood Collection and Processing. The procedures are almost identical to the CT; specifically, blood drawn for local lab analyses and for specimen repository are required for OS women. The local lab has a lower priority. Attempts should be made to collect the blood for McKesson Bioservices before collecting the local blood. It is important that **fasting** blood is obtained. If a woman is not fasting at the time of the clinic visit, she should be given another clinic appointment so that fasting blood can be obtained. At least 2 ml. of must be obtained for a participant to be eligible for OS enrollment. This means that a minimum of 4 ml. of blood must be drawn into a royal blue tube (to make 2 ml. of serum). Thus, at least two aliquots should be sent to McKesson Bioservices (1 ml. each in cryovial, 02 and 03).

The following additional CC procedures and questionnaires are required for OS participants at Bone Densitometry CCs:

Form 87 - Bone Density Scan

Form 101 - Urine Collection and Processing

In order to limit study costs and the burden on the participant and CC staff, baseline OS procedures and questionnaires that need to be done at a CC visit should be completed at SV1 if possible. OS participants do not need any further screening visits once the baseline CC requirements have been satisfied. Clinical Centers should try to keep the need for further CC visits to complete baseline OS procedures to a minimum by:

1. Completing the CC procedures and CC-administered questionnaires required for OS participants at SV1 and not assuming that procedures can be delayed until a subsequent screening visit.
2. Ensuring that women come to screening visits prepared for procedures. This means that they should be fasting (for fasting blood draw), dressed in suitable clothes (for physical measurements), and should be reminded to bring all medications and supplements (to enable the completion of *Task 44 - Current Medications* and *Task 45 - Current Supplements*).

The following CC tasks required for CT participants are **NOT required for OS participants**:

Form 39 - Cognitive Function

Form 81 - Pelvic Examination/Pap Smear (HRT)

Form 82 - Endometrial Aspiration (HRT)

Form 84 - Clinical Breast Exam

Form 85 - Mammogram

Form 86 - ECG

Form 90 - Functional Status

However, if any of these procedures have been completed before the participant enrolls in the OS, the information should be entered into WHILMA.

8.3.2 Self-Administered Questionnaires

The following self-administered questionnaires are required on all OS participants:

Initial Consent - (and *Form 11 - Consent Status* indicating that the OS Consent Form has been signed.)

OS Consent - (and *Form 11 - Consent Status* indicating that the OS Consent Form has been signed.)

Form 20 - Personal Information

Form 30 - Medical History

Form 31 - Reproductive History

Form 32 - Family History

Form 34 - Personal Habits

Form 37 - Thoughts and Feelings

Form 42 - Observational Study Questionnaire

Form 60 - Food Frequency Questionnaire (FFQ)

Self-administered questionnaires can be administered in several ways (or a combination of these):

1) Mailed before SV1 to be completed at home and returned at SV1. This option can <u>not</u> be used for *Form 37*.

2) They can be completed by the participant at the CC during the CC visit if time and space permit. This method is preferable so that the participant is able to ask the CC staff questions about any of the forms, and to ensure that questionnaires are completed and returned to the CC.

3) They may be given to a woman at a clinic visit to complete at home and mail back to the CC, or returned at the time of the next CC visit (if CC procedures are incomplete). Participants who are to complete the self-administered questionnaires at home should be provided a postage-paid, addressed envelope in which to mail the questionnaires to the clinic, and should be given the name and phone number(s) of the CC staff member(s) to call with questions.

4) Women who have completed the CC visit procedures and questionnaires (see *Section 8.3.1 - Questionnaires and Procedures Administered at a CC Visit*), do not need to return to the CC to enroll in the OS. The self-administered questionnaires not yet complete may be mailed to the woman along with a cover letter including the name(s) and phone number(s) of CC staff members to call with questions and the return envelope. A sample cover letter is included in *Appendix E, Figure E.6.1* - As noted in *Section 8.2.4 - Entry Into OS Outside a CC Visit*, this packet would also include the OS Consent and other material.

See *Vol. 3 - Forms* for detailed instructions on completing each of the baseline forms.

The following questionnaires are **NOT required for OS participants**:

Form 4 - HRT Washout (HRT)

HRT Consent (HRT)

DM Consent (DM)

CaD Consent (CaD)

Form 53 - HRT Calendar (HRT)

Form 62 - Four-Day Food Record (4DFR) (DM)

However, if any of these questionnaires have been completed before the participant enrolls in the OS, the information should be entered into WHILMA.

8.3.3 Procedures for Questionnaires Not Returned to CC

Each CC should develop an approach that leads to the required collection of data from the women. The follow-up procedures should not be so aggressive that non-compliant women enter the OS. Suggested follow-up procedures include:

1. A postcard after one week to all women who were given questionnaires to return. The text on the postcard should have a combination thank you/reminder message (e.g., "thank you for returning the questionnaires" and "if you haven't returned them yet, please send them back soon"). A sample postcard is in *Appendix E, Figure E.6.2*.

2. A telephone call after three weeks to women who have not returned all forms. On this call, speak to the woman (rather than leave a message), ask her to complete and return the forms, and ask if she needs new forms mailed to her. Mail new forms if requested. For a sample telephone script see *Figure 8.2*.

8.3.4 Maximum Time for Completion of Baseline Data

For women whose SV1 is on or **after** September 1, 1994, all forms and procedures must be complete within six months after SV1 (excluding *Form 2/3 - Eligibility Screen*, and *Form 60 - FFQ*).

For women screened by VCCs **before** September 1, 1994, all forms and procedures must be completed within one year after their SV1 visit (excluding *Form 2/3 - Eligibility Screen*, and *Form 60 - FFQ*).

8.3.5 Quality Assurance Procedures

Quality assurance procedures associated with the OS forms and procedures are the same as those for the CT. Before the participant leaves the CC do a final check that she has signed the OS Consent, and that all baseline CC procedures have been completed. Review all completed self-administered questionnaires for completeness; if one or more pages are missing, return to the woman to complete. Do not return to the woman

if it appears that she has purposely refused to answer questions of a sensitive nature. Forms mailed to the CC should be reviewed in the same manner with telephone callbacks to the woman when necessary to complete the information on the form.

8.3.6 Ending the OS Baseline Visit

Participants in the OS may be seen in the CC only once during screening and will not usually be seen again until three years after the baseline information is obtained. Thus, efforts to maintain their interest in WHI and ensure retention and follow-up will be very important. Before the end of the final OS baseline visit the participant should be given an outline (verbal and/or written) of what to expect and what will be requested of her during the course of the OS. Explain the importance of future participation. Make sure that the participant has a phone number for the CC. Ask her to notify the CC if she moves to a different address. For women enrolling outside a clinic visit, this information can be provided by mailed materials (cover letter, OS Consent, "Welcome to the OS" handout).

8.3.6.1 Annual Newsletters

Inform the participant that she will start receiving yearly newsletters within the next 12 months, and that they will arrive at about the same time each year. Tell her that the purpose of these newsletters will be to keep her informed of the progress of the study, and to verify her address through the post office.

These newsletters will be mailed to the CCC at six months post-enrollment, with the return address of each CC. It is the responsibility of the CC to update the database in the case of a change of address.

8.3.6.2 Yearly Update Questionnaires

Inform the participant that each year she will receive a few questionnaires from the CC, starting one year from the date that she enrolled in the study. Tell her to expect these questionnaires at the same time each year, about the time of the anniversary of her enrollment in the OS. Inform her that she should complete these questionnaires and mail them back to the CC in the enclosed pre-paid envelope as soon as possible after receiving them. Reassure the participant that completing the three yearly update questionnaires will be a lot less work than the baseline questionnaires, and outline what these questionnaires will be about.

- The medical history update questionnaire will ask the participant to report the occurrence of important medical problems such as hospitalization, heart attack and heart disease, stroke, cancer and fractures.
- The OS update questionnaire will ask for updated information on things such as hormone replacement therapy, which may affect her risk of developing certain medical conditions.

Every few years the participant will also receive a personal information sheet listing information such as her telephone number, address, and health care provider. She will be asked to update and return the sheet to the clinic if there are any changes to the personal information listed.

8.3.6.3 Future CC Visits

For CCs that are not Bone Densitometry CCs, inform the participant that she will be asked to return to the CC for a visit at the 3-year anniversary date. Explain to the participant that the procedures and measurements done at the 3-year CC visit will be similar to those done at the baseline CC visit(s). Before her visit, the CC will mail a packet of questionnaires for her to complete and bring to the visit. Procedures at the CC visit will include some physical measurements such as blood pressure and weight, and a blood sample will be drawn.

For Bone Densitometry CCs, inform the participant that she will be asked to return to the CC at 3, 6, and 9 years after her enrollment into the OS. OS participants attending one of the Bone Densitometry CCs will have their bone density measured at the follow-up visits and will be asked to provide a sample of urine, in addition to the other procedures (questionnaires and physical measurements).

8.3.6.4 Arranging Follow-Up for OS Participants

After the participant has completed the baseline questionnaires and procedures listed above, her baseline OS activities are completed. At this point, you should verify that her current address is accurate and she is not planning to move within the year. If she routinely is away at the time she would receive either the yearly newsletter or the yearly follow-up questionnaires, ask for that address as well. Thank her for her participation in the study. Explain to the participant that it is very important to obtain complete follow-up information on all participants in order to ensure that the results of the study are valid and scientific. Check that she has the CC's phone number. If the participant has not completed all the self-administered OS baseline questionnaires by the end of the OS Baseline CC Visit, check that she has a copy of each of the outstanding questionnaires and a return mailer. Advise her to contact the CC if she has questions concerning the completion of these questionnaires, and ask her to mail the completed questionnaires to the CC as soon as possible.

Provide the woman with the "Welcome to the OS" handout, the membership ID card, and the WHI magnet. The CCs have the option of also providing health education materials (e.g., BSE shower card, health pamphlets) as incentives.

8.3.7 Enrolling Women in the OS

When a woman has completed the OS Consent and all of the OS tasks, enroll her into the OS. To be enrolled, a woman must meet the eligibility requirements; *Form 2/3*, *Form 6*, and *Form 11* must be complete; and the woman must have completed all of the required forms and procedures listed in *Section 8.3.1 - Questionnaires and Procedures Administered at a CC Visit* and *Section 8.3.2 - Self-Administered Questionnaires*. To enroll a woman in the OS, invoke the enrollment function in WHILMA as described in *Vol. 5 - Data System, Section 6.3 - OS Enrollment*.

8.3.8 Reporting Abnormal Findings

Abnormal findings on blood pressure or CBC must be reported to the women and her physician or clinic. See *Sections 4.2.7.1 - Blood Analysis Results* and *9.2.6 - Alert Values* [for BP] for the procedures.

8.3.9 Baseline Procedures on Participants Who Have Completed Part of the Screening Process Before September 1994

At the start of the OS in September 1994, VCCs should give priority to recontacting women who have attended SV1 (with or without SV2 and SV3) before the start of the OS, but who did not enroll in the CT. All such women should be recontacted as soon as possible after the start of the OS and invited to participate in the OS (see *Figure 8.1* for sample telephone script). If the woman agrees to participate in the OS, efforts should be made to complete the outstanding baseline questionnaires and procedures within as short a time period as possible. (This urgency does not apply to participants who completed prescreening activities [or SV0s] but did not attend SV1 before the start of the OS.)

For women who have completed the CC visit tasks outlined in *Section 8.3.1 - Questionnaires and Procedures Administered at a CC Visit*, the procedures for entering these women are similar to those in *Section 8.2.4 - Entry Into OS Outside a CC Visit.* A sample cover letter for enrolling women who completed the screening process prior to 9/1/94 is in *Appendix E, Figure E.6.3.*

If a woman has not completed the CC visit tasks outlined in *Section 8.3.1 - Questionnaires and Procedures Administered at a CC Visit*, she should be invited for another CC visit to complete the remaining tasks. The procedures for entering these women are similar to those for other women entering the OS during a clinic visit.

In addition, for <u>all</u> women who completed self-administered questionnaires before September 1994, certain forms must be updated after September 1, 1994. These include *Form 2/3, Form 20, Form 30, Form 31, Form 32*, and *Form 34*. *Form 60* and *Form 37* do not need to be updated and should not be given to the woman unless she has never completed these forms. *Form 2/3* should be updated at the telephone call during which the woman is invited to enter the OS.

There are several ways to update the other forms depending on whether the old forms are still available or not, have been entered into the database or not, or are mark-sense forms or not. One option is to send new forms to the woman in the packet with the OS Consent and the questionnaires not yet completed by the woman. The instructions should state that even though she has already completed some of these questionnaires, we need her to fill them out again.

Another option for forms that have been entered into the database before a woman enrolls in the OS is to mail the actual forms the woman has **already completed** to the woman (in the packet with the OS Consent and other forms not yet completed). (The OMB number and text need not appear on the forms.) She should be asked to review these forms, make any changes with a red pen (which should be included in the packet) and return all forms with the OS Consent to the CC. (A post-it note on these forms saying "Use red pen" may be helpful.) After the old forms are returned, change the date on these forms to be the date the forms were returned to the CC, whether or not any changes were made by the women. Edit the new date and any changes into the database, when the forms are returned. This option is also best for mark-sense forms. They should be scanned before mailing them back to a woman if they have not been already.

Finally, for forms that are not mark-sense forms and that have not yet been entered into the database, the forms can be mailed to the woman to update (no red pen needed). Then after the date on the forms has been changed to be the date received by the clinic, the entire form can be entered into the database.

Whichever option is used, it may be helpful to send the woman a Questionnaire Description Sheet (*Appendix E, Figure E.6.4*). On this sheet, you can indicate which forms need to be completed and which need to be updated.

8.4 OS Measurement Precision Study - OS-MPS

The OS Measurement Precision Study (OS-MPS), as discussed in *Vol. 1 - Study Protocol & Policies*, will include a subsample of 1,000 women randomly selected from among new OS enrollees. The women chosen to participate in this study will be asked to repeat four of the questionnaires from the baseline CC visit approximately 10 weeks after OS enrollment and return to the CC in order to have their blood drawn. The OS-MPS will provide critical scientific data about the reproducibility of measures such as physical activity and reproductive history from the self-administered questionnaires, and will provide repeat fasting blood samples to test the accuracy of future blood measures.

8.4.1 Participants

One thousand women will be invited to participate in the OS-MPS from among women who enrolled in the OS during the period of September 1, 1996 to May 30, 1997. At each of the forty CCs, twenty-five participants will be randomly selected from among new OS enrollees to participate in this study. CCs should be sure to inform all OS participants enrolled during this time that there is the possibility they may be invited to participate in the OS Measurement Precision Study. This study is described in the model OS consent under "What Will You Be Doing?" The first list of participants selected for the OS-MPS will be identified on the *OS-MPS Participant Status Report* that will be mailed to CCs on or about October 15, 1996.

For each of the first five months of enrollment during the OS Measurement Precision study period, approximately five participants from each CC will be selected. Additional participants may be selected in the last four months of this period to account for non-response and variations in sampling. Please note that each CC is required to **enroll** into the OS-MPS twenty-five participants who complete the four questionnaires and have a blood draw. To meet this enrollment goal, the CCC will select more than twenty-five participants, depending upon the number of randomly selected women who decline to participate. The selection of OS-MPS participants will be stratified by both ethnicity and age.

8.4.2 Forms

The subset of questionnaires that each participant in the OS-MPS will be asked to repeat is determined by the group to which your particular CC has been randomly assigned (see list below). Each woman participating in the OS-MPS will repeat four of the questionnaires she completed during her screening visits and return to the CC to have her blood drawn.

The following lists specify the questionnaires and procedures that will be completed by the OS-MPS participants at the CCs assigned to Group A or Group B:

Group A:	**Group B:**
Form 2 *- Eligibility Screen* (selected questions; to be self-administered even if *Form 3* was used at baseline)	***Form 20*** *- Personal Information* (selected questions)
Form 30 *- Medical History Questionnaire*	***Form 31*** *- Reproductive History Questionnaire*
Form 37 *- Thoughts and Feelings*	***Form 32*** *- Family History Questionnaire*
Form 42 *- Observational Study Questionnaire*	***Form 34*** *- Personal Habits Questionnaire*
Form 100 *- Blood Collection and Processing* (completed by CC Staff)	***Form 100*** *- Blood Collection and Processing* (completed by CC Staff)

The following are the CCs assigned to Groups A and B:

Group A CCs**:**	***Group B CCs:***
Atlanta	Birmingham
Boston	Chapel Hill
Bowman Gray	Chicago
Buffalo	Columbus
Chicago-Rush	Detroit
Cincinnati	GWU
Gainesville	Irvine
Honolulu	Memphis
Houston	Miami
Iowa City	Milwaukee
La Jolla	Minneapolis
Los Angeles	Nevada
Madison	Newark
Medlantic	Oakland
New York	Pawtucket
Pittsburgh	San Antonio
Portland	Seattle
Tucson	Stanford
UC Davis	Stony Brook
Worcester	Torrance

8.4.3 Procedures

The procedures for the OS-MPS are identical to those performed during the baseline CT and OS visits with two expections. First, failures or refusals for the blood draw are acceptable—the participant does not need to return for a repeated attempt to draw her blood. Second, all questionnaires must be completed before or at the CC visit scheduled for the OS-MPS blood draw. The questionnaires may not be sent home to be completed after the OS-MPS visit. At each CC, 20 of the 25 participants must complete the forms/blood charts; up to five may agree to complete only the required forms.

The following are the procedures to recruit women into the OS-MPS and to complete the study:

1. Beginning in October 1996, the CCC will send the *OS-MPS Participant Status Report* to each CC via the weekly FedEx. This report will list at least five OS-MPS participants who have been randomly selected from OS enrollees. This report will also serve as a dispositions record and needs to be mailed back to the CCC to update the status of all CC OS-MPS participants.

   Each month, the CCC will also supply the CCs with the necessary cover letters and forms, including Spanish forms and cover letters, if appropriate (based on the WHILMA "Spanish Flag"). Note that the CCC will include alternate versions of the cover letter to use for participants who only agree to complete the forms but not return for the blood draw (in addition to the full cover letter versions and questionnaires). A sample containing the text of the cover letter is given in *Figure 8.4 - OS-MPS Cover Letter*. If you prefer to mail participants the cover letter on your own stationary, use the electronic model letter emailed to the clinic managers on September 6, 1996.

   If you have a satellite clinic, the OS-MPS packet, for both will be mailed to the primary and satellite clinics, respectively.

   Additional packets of questionnaires will be provided by the CCC to allow for participants who forget to bring their completed questionnaires with them to the CC.

2. Over the course of the next four weeks, after receiving the list of participants, each CC will contact these participants by telephone to inform them of their selection and explain the purpose and procedures of the OS-MPS. Remind the participant that her participation is voluntary and that she has the right to decline without affecting her continued participation in the OS. Explain that the study includes repeating four questionnaires at home and returning to the CC for another fasting blood draw. Emphasize that we will gain important information about how reliable our questionnaires are (do not say ". . . how reliable your responses are"). For a sample telephone script, see *Figure 8.3*.

   For each woman who agrees to participate, schedule an appointment for a return visit to the CC for a date approximately 10 weeks (range: 8-15 weeks) after her enrollment in the OS. If a participant who has been selected to join the OS-MPS refuses to return to the CC for the repeat blood draw, you must still invite her to participate in the study by completing the questionnaires and mailing them back to the CC. The *OS-MPS Participant Status Report* will identify the date by which the visit must be completed.

3. Two weeks before her scheduled appointment, mail a packet that includes the questionnaires to be repeated and the appropriate cover letter (both furnished by the CCC).

   The questionnaires in the packets are identical to those completed during screening and before OS enrollment. The packet sent to participants from Group A CCs will contain a *Form 2* that has been marked (by the CCC) to exclude certain questions participants are not required to repeat. Similarly, Group B CCs will be sending out packets that contain a *Form 20* that has been marked (by the CCC) to exclude certain questions. All OS-MPS forms will be marked as a "non-routine" visit type by the CCC.

   Mail the packets of questionnaires to the participant **via first-class mail**. Include the following in the envelope:

- the standard cover letter -- write in the place, date, and time of the participant's appointment as well as the telephone number of the CC, sign the letter, and insert it into the packet

  For those participants who refuse to return to the CC for a blood draw, insert the alternate cover letter into the packet. Write in the telephone number of the CC and sign the letter. Add a stamped, self-addressed envelope in which she can return her questionnaires.

- the four questionnaires, and
- a No. 2 pencil to be used when filling out the mark-sense forms

4. The day before a participant's scheduled visit, call her to remind her of the visit time (optional) and to fast for 12 hours before the visit.

5. At the OS-MPS visit, do the fasting blood draw and collect the completed questionnaires. If the participant arrives without the completed questionnaires, ask her to fill out the questionnaires at the visit. The CCC will have sent extra packets of questionnaires to CCs for this purpose. If the participant says that she has already completed the forms but left them at home, you may give her a stamped, addressed envelope in which she can return her questionnaires. Ask her to mail the questionnaires within 24 hours of the visit.

   Review the questionnaires for completeness as you would have done during screening procedures. Refer to *WHI Manual - Vol. 2, Section 4 - Screening* and IRS #96-0198.

   The CC should follow-up on any participant who schedules a return visit to the CC and then fails to show up at the appointed time. Call these participants within 48 hours to reschedule an appointment for them. If a participant is unable or unwilling to make a return visit to the clinic, ask that she still participate in OS-MPS by filling out the packet of questionnaires and returning them to the CC by mail. Send her a stamped, self-addressed envelope in which she can return the completed questionnaires.

6. Thank the participant for the effort she has put into this study.

7. When completed forms are collected, check to make sure the visit type on all forms is marked as "non-routine" (including *Form 100 - Blood Collection and Processing*).

8. Collect and process the blood in the usual manner, including the local analyses of blood.

9. Enter the data into WHILMA in the usual manner. Note that the visit type should be "non-routine." For CCs in Group B, please note that data screens for *Form 20* will not be altered to remove the questions the women are asked not to answer. Care is advised during data entry of *Form 20*.

10. Record the disposition of each participant on the *OS-MPS Participant Status Report*, indicating if she had declined the blood draw, the forms completion, or both, when you have completed recording the disposition for each woman on the report, mail the report back to the CCC.

8.5 Follow-Up Procedures for OS Participants

OS participants will be followed up by annual newsletters, an annual mail contact to collect Medical History Updates, and a third-year CC visit (at which time the baseline clinical measurements will be repeated).

8.5.1 Annual Newsletter

All OS participants receive a trial-wide WHI newsletter (*WHI Matters*) once a year during the sixth month after their enrollment month. The goal of the newsletter is to present news about WHI, promote retention, and to keep up-to-date addresses for participants. For a detailed description of the newsletter and procedures for updating addresses for undeliverable newsletters, refer to *Section 17.1.5 - Participant Newsletter*.

8.5.2 Annual Mail Contact

Follow-up data (Medical History Update and exposure information) are collected annually from OS participants during the nine years following enrollment. Activities to collect the data consist of a series of mail and telephone contacts during the follow-up period. Data collection attempts by mail are conducted by the Clinical Coordinating Center (CCC) on an annual basis, except during the participant year 3 when data are collected by the CC during the follow-up clinic visit. For a full discussion of procedures, refer to *Section 16.5 - OS Annual Mail Contact and Follow-Up of Non-Responders*.

8.5.3 Follow-Up of Non-Respondents

For participants who do not respond to the CCC's annual mailed contacts, data collection attempts by telephone are conducted by the CCs on an every other year basis. Refer to *Section 16.5.3 - CC Data Collection for Non-Respondents to OS Mailings*.

8.5.4 Three Year Visit to CC

Clinic Visits are conducted for OS participants in the third year following enrollment. Refer to *Section 16.3 - Annual (CT) and Third Year (OS) Visit* for a description of the procedures and activities for this visit.

Figure 8.1

Telephone Script for Enrolling OS Women by Mail
(For Those Who Have Completed OS Screening Tasks That Require a CC Visit)

"Hello Ms./Mrs. _____, this is _____ from the Women's Health Initiative (name of clinical center) ."

For women who became ineligible for the CT between screening visits:

"We have reviewed the forms and results of the tests you recently completed during your visit to our Clinical Center. Based on these results, we have found that you are eligible to join the health tracking or "Observational" part of the study."

If woman asks for reason for ineligibility, give her the reason if that is your clinic's policy. If not:

"There are many considerations that go into the decision as to whether or not you are eligible to join the study. We take all of the information we have collected on you - your physical measurements, health history, medication and hormone use, and dietary habits and enter it into the computer. The computer has a formula that considers all of this information and determines whether you are able to join the study."

For women who are not interested in joining the CT:

"We have reviewed the forms and results of the tests you recently completed during your visit to our Clinical Center. We understand that you are not interested in joining the Hormone or Dietary Studies, so we would like to invite you to join the health tracking or Observational Study instead."

For women who were screened months ago and were found to be ineligible for CT:

"We have reviewed the forms and results of the tests you completed some time ago during your visit to our Clinical Center. Your results indicated that you were not eligible to join the parts of the study going on at that time. Since that time, we have started the health tracking or "Observational" part of the study, and would like to invite you to join."

Continue for all women:

"The purpose of the Observational Study is to learn more about women's health in general and about the causes of disease in women. If you join the Observational Study, first we will send you questionnaires for you to complete at home. Then once a year for the next 8-12 years we will mail you health updates that consist of three short questionnaires. You will fill these questionnaires out in your home, and return them to the Clinical Center in the postage-paid return envelope provided."

For women not at bone density sites:

"In addition to filling out these questionnaires, you will need to come in for another clinic visit in three years. During this visit, you will have similar procedures and measurements as those done at the screening visit. There will be some physical measurements such as height and weight, and a blood sample will be drawn."

For women at bone density sites:

> "In addition to filling out these questionnaires, you will need to come into the clinic every three years for tests similar to the ones you have already done. This means that you will come into the clinic for three more visits: one in three years, one in six years, and one in nine years. This includes physical measurements such as height and weight, and a blood sample will be drawn. You will also have your bone density measured and will be asked to provide a urine sample."

Continue for all women:

"We plan to enroll a total of 100,000 women from all over the U.S. in this study. We want the results of this study to represent all women, so if you're interested, we'd really like you to join. Can we send you the questionnaires for the Observational Study?"

If no:

> "I'm sorry that you won't be able to join the study. I would like to thank you very much for your interest in the Women's Health Initiative and for the time you have already spent in the study. If you should change your mind, please give us a call at the Clinical Center and we'll see about enrolling you in the study. Thanks again for your time."

If yes (and screened after Sept. 1):

> "Great! In the next few days we'll be sending you a packet containing the materials you will need to become a member of the Observational Study. In the packet you will find several items, including consent forms, several health questionnaires, and a postage-paid envelope. When you receive this packet, you will need to sign the consent forms, fill out the health questionnaires, and mail everything back to us in the stamped envelope. There will be instructions included in your packet that explain this in greater detail."

If yes (and screened before Sept. 1):

> "Great! In the next few days we'll be sending you a packet containing the materials you will need to become a member of the Observational Study. In the packet you will find several items, including consent forms, new health questionnaires, a copy of some of the questionnaires you filled out already, and a postage-paid envelope. When you receive this packet, you will need to sign the consent forms, fill out the new health questionnaires, and review and update the old questionnaires. Then you will need to mail everything back to us in the stamped envelope. There will be instructions included in your packet that explain this in greater detail."

Continue for all women:

"Do you have any questions?"

Answer any questions, then wrap it up:

"In about six months we'll send you a copy of the WHI newsletter to help keep you informed about the progress of the study. This newsletter will arrive every year for the next 8-12 years. Also, in one year you will receive the health update questionnaires mentioned earlier, which you will complete and mail back to the clinic. In about three years we'll give you a call to let you know that it's time to come in for your three year visit."

"We appreciate your interest in the Women's Health Initiative. Please call us when you receive your packet if you have any questions about filling out your forms, or if you have any questions about the study in general. Thank you for your time."

Figure 8.2

Telephone Script for Follow-Up Reminder to OS Women
(For Those Who Have Not Returned Their Questionnaires by Three Weeks Post-Mailing)

The caller should telephone until she/he is able to reach the woman. If woman is unavailable, leave a message with a relative or on a machine for her to call the clinic.

"Hello Ms./Mrs. _____, this is _____ from the Women's Health Initiative (name of clinical center) ."

If packet mailed:

"A few weeks ago a packet of questionnaires was given to you or mailed to you from the Women's Health Initiative. Did you receive the packet?"

If no:

"I'm sorry to hear that." (***if mailed:*** "Perhaps it was sent to the wrong address.") "Let me confirm your mailing address so that we can send you out another packet."

(Confirm address, thank participant, terminate call, mail new packet.)

If yes:

"Good! Have you had time to complete the questionnaires?"

If yes:

"Great! Thanks very much for your quick response. Could you please return the materials to us right away in the postage-paid envelope? This would include one copy of the consent form with your signature and the completed health questionnaires. We can't officially enroll you in the study until we have received all of your materials."

(Participant response)

"Thank you very much for your time and for your interest in joining the Observational Study. We're very glad to have you as part of the study."

If no:

"Do you have any questions about the forms that I could answer for you?"

If yes, answer questions, then continue:

If no, continue:

"Could you please fill out the forms as soon as possible and return them to us here at the Clinical Center? We can't officially enroll you in the study until we have received all of your forms."

(Participant response)

"Thank you very much for your time and interest in joining the Observational Study of the Women's Health Initiative. We're very glad to have you as part of the study."

If at any point she indicates that she does not want to join the Observational Study (enter as refusal):

"I'm sorry that you won't be able to join the study. I would like to thank you very much for your interest in the Women's Health Initiative and for the time you have already spent in the study. If you should change your mind in the next few weeks, please give us a call at the Clinical Center and we'll see about enrolling you in the study. Thanks again for your time."

Figure 8.3

Telephone Script for Contacting OS Women to Participate in OS-Measurement Precision Study

The following is a suggested script that can be used when contacting OS participants:

"Hello Ms./Mrs._____, this is _____ from the Women's Health Initiative [name of clinical center]. As you may remember when we explained the Observational Study to you, some women who enroll will be invited to return to the clinic to repeat some measurements from the original visit. This repeat visit is very important because it will help us test how accurate and reliable our WHI forms are in collecting research information. You are one of the women who has been selected at random by the computer to return to the clinic for this repeat visit."

"Your participation in this repeat visit is voluntary and you have the right to decline without affecting your participation in the Observational Study. If you do agree, we will mail you four of the questionnaires you completed before and ask you to complete them again at home. We will then schedule a return visit to the clinic. At that visit we will collect the forms you completed and you will have another fasting blood draw. That is all we would need; none of the other procedures or forms will be repeated. The clinic visit will take approximately _____ [amount of time relative to your clinic-specific procedures]."

"Do you have any questions? Are you willing to do this repeat visit?"

For women who specifically refuse to return to the CC for the repeated blood draw:

"If you don't want to return to the clinic for the blood draw, would you be willing to help us by just completing the four questionnaires and mailing them back to the clinic? [If yes, mail her the forms with a self-addressed, stamped envelope. Continue to "all" script. If no, continue to script for "women who are not interested in joining the Measurement Precision Study."]

For women who are NOT interested in joining any of the Measurement Precision Study:

"We do appreciate all you've done so far in the Observational Study. Remember, your decision doesn't affect your participation."

For women who are interested in joining the Measurement Precision Study:

"Great! Let's schedule an appointment for your repeat clinic visit. [Schedule a convenient appointment.] Your return visit to _____ is scheduled for _____ at _____ . I will mail you the forms to complete. You should receive them within the next week. It is important that you try to complete the forms before you come to the clinic for your appointment. We look forward to seeing you again."

ALL

"We are so glad you are a part of the Women's Health Initiative. Thank you very much for your time."

Figure 8.4

OS Measurement Precision Study Cover Letter

Dear Participant:

Thank you for being part of the Measurement Precision Study of the Women's Health Initiative! As a participant in the study you are being asked to repeat four of the forms you filled out during, or before, your recent visit to our clinical center. This study will provide scientific information on how well the forms used in the Women's Health Initiative are working.

(PARAGRAPH FOR CCs in GROUP A) Please complete the enclosed four forms, using the #2 pencil we have provided. *Form 2 - Eligibility Screen* is a version of the form you filled out before joining our study. To reduce the number of questions you have to answer, several questions on this form have been crossed out. You do not need to answer those questions. *Form 30 - Medical History Questionnaire* asks about your history of hospitalizations and medical conditions. *Form 37 - Thoughts and Feelings* asks about your social relationships, feelings and experiences. *Form 42 - Observational Study Questionnaire* asks about your habits and lifestyle.

(PARAGRAPH FOR CCs in GROUP B) Please complete the enclosed four forms, using the #2 pencil we have provided. *Form 20 - Personal Information* asks for information about your age, education, and occupation. To reduce the number of questions you have to answer, several questions on this form have been crossed out. You do not need to answer those questions. *Form 31 - Reproductive History Questionnaire* requests information about your pregnancies and reproductive health. *Form 32 - Family History Questionnaire* contains questions about members of your family and diseases that your relatives may have had. *Form 34 - Personal Habits Questionnaire* asks about your health habits, such as smoking and exercise.

(PARAGRAPH 1 AND 2 (FOLLOWING) FOR ALL WOMEN WHO DO ACCEPT THE BLOOD DRAW) Remember to bring your completed forms with you when you return to have your blood drawn. Your return visit to_____

is scheduled for _____ at _____.

This visit is to draw a fasting blood sample as part of our Measurement Precision Study. It is important that you take no aspirin or anti-inflammatory drugs (prescribed or over-the-counter for example, ibuprofen, Advil, or Motrin) for 48 hours before the clinic visit and have nothing but water to eat or drink during the 12 hours before the clinic visit. If you usually take medications other than aspirin or anti-inflammatory drugs in the morning, you may take them with water at the usual time. You should not take medicines for diabetes until after the blood draw, unless your doctor has given you other instructions. During the 12 hours before your clinic visit, you should also not do any vigorous exercise. In addition, you should not smoke for one hour before your blood draw.

(ALTERNATE PARAGRAPH FOR WOMEN WHO DO NOT ACCEPT TO DO THE BLOOD DRAW) Please mail the completed forms back to us in the enclosed return envelope. If you have any questions, please call us at _____.

As always, all information you provide will be kept confidential and your name will not be linked with data given to anyone other than the researchers in this study. Participation in this study is voluntary and you may refuse to answer any questions on the forms. However, it is very important to have complete information on all participants in our Measurement Precision Study to make sure that the results are accurate and scientific.

We appreciate your participation in this special part of the Women's Health Initiative. This is an important part of our efforts to improve the health of women for generations to come. Every woman counts, so please be sure to complete these questionnaires carefully and completely.

We look forward to seeing you again! If you need to change your appointment time or have any questions, please call us as soon as possible at _____.

Sincerely,

Section 8
Observational Study

Table of Contents

CLINICAL MEASUREMENTS

INTRODUCTION

Participants have clinical measurements performed at many different visits. This section describes how each measurement should be done, regardless of the visit at which they're done. Some general guidelines include:

- Ensure Clinical Center (CC) staff are appropriately trained and certified to perform specific Women's Health Initiative (WHI) clinical measurements (required).
- Evaluate carefully CC staff's expertise, training, and state licensure guidelines to determine who should perform specific measurements (recommended).
- Cross-train and certify CC staff on several measurement procedures to allow maximum flexibility in CC operations (recommended).
- Record all measurements in metric units (required).
- Maintain measurement equipment in good working order (required).
- Make arrangements for appropriate back-up equipment either on-site or from equipment suppliers or service representatives (recommended).

The routine of the CC over time will encourage familiarity with clinical measurement procedures. These measurements are an important aspect of the study and the collection of this information must be done with a sense of care and excellence.

9.1 Resting Pulse (Required)

Clinical Trial (CT) and Observational Study (OS) participants have a resting pulse determination during screening and follow-up visits as outlined in *Vol. 1 - Study Protocol and Policies, Table 1-A1.1 - Frequency of Data Collection*. Perform this procedure before (or at least 30 minutes after) other potentially stressful procedures (e.g., blood draw or weight measurement). The pulse should be measured in a quiet area away from other CC activities. Have a table next to the chair where the participant sits. Have the participant sit quietly with both feet flat on the floor without smoking or talking for a 5-minute rest period before taking the pulse measurement. A clock or watch with a second-hand or a stopwatch is required for this procedure. The pulse measurement can immediately precede the blood pressure (BP) measurement without a rest period in between if the arm circumference measurement for BP is done before this rest period [see *Section 9.2 Blood Pressure (Required)*].

9.1.1 Training and Certification

Women's Health Initiative (WHI) CC staff can perform the resting pulse measurement after completion of the WHI training and certification process.

9.1.2 Performing the Measurement

Instruct the participant to rest her elbow and forearm comfortably on the table. The resting pulse is usually measured at the radial artery. With the participant's palm turned upward, use the pads of your index and middle fingers to palpate the radial artery until a maximum pulsation is detected. Count the pulse for 30 seconds using the second-hand of a watch or clock or setting a stopwatch at 0. Record the number of beats in 30 seconds on *Form 80 - Physical Measurements*. Then, multiply the number by two and record that result also on Form 80 Inform the participant of her resting pulse measurement.

9.1.3 Alert Values for Resting Pulse

Refer participants with a markedly irregular pulse or a resting pulse rate of less than 40 beats/minute or greater than 130 beats/minute to your Clinic Practitioner (CP). Check your CC guidelines for any CC-specific alert actions for the resting pulse measurement.

9.2 Blood Pressure (Required)

Clinical Trial and OS participants have BP determinations during screening and follow-up visits as outlined in *Vol. 1 – Study Protocol and Policies, Table 1-A1.1 – Frequency of Data Collection*. A conventional mercury sphygmomanometer, appropriate-sized BP cuffs and stethoscope with a bell are required for this procedure. If you are using a non-mercury manometer due to institutional biohazard requirements, notify the CCC of the name/model number of the equipment being used and the exact date the equipment was implemented. The procedures documented below pertain to a mercury manometer. Also needed are a clock or watch with a second-hand or a stopwatch for this procedure. Perform this procedure before (or at least 30 minutes after) other potentially stressful procedures (e.g., blood draw or weight measurement). Although it is recommended that the BP be measured before the blood draw, if this is not possible, do the two procedures in opposite arms (e.g., left arm for blood draw, right arm for BP), allowing sufficient time (e.g., 30 minutes to one hour) to pass after the blood draw and before the BP measurement. If the BP is measured right after the pulse and a sufficient rest period precedes the pulse, it is not necessary to rest again between the pulse and BP measurements (as long as arm circumference is measured before the rest period). The BP measurement area should be free of excessive noise and the participant should not be interviewed at this time. Obtain two sitting systolic and diastolic BP measurements using a conventional mercury sphygmomanometer and record the results on *Form 80 – Physical Measurements*.

It is advisable to have an additional conventional mercury sphygmomanometer and standard stethoscope available in the CC in case of an equipment failure.

9.2.1 Training and Certification

Women's Health Initiative CC staff can perform the BP measurements after completion of the WHI training and certification process.

9.2.2 Blood Pressure Procedures

The BP measurement is based upon the combined principles of compression of the brachial artery under an elastic, inflatable cuff and direct registration of pressure levels by a manometer. The observer inflates the appropriate-sized cuff placed on the participant's upper arm, listens for the first (systolic) and the last (diastolic) Korotkoff sounds, reads the level in the column, deflates the cuff, and records the readings.

9.2.2.1 Blinding

The CC staff person performing the BP measurement is automatically blinded at the baseline visit because the BP measurement is done before randomization to a treatment group. At each annual follow-up visit, the BP measurement should be performed without knowledge of the participant's treatment assignment or previous visit's BP measurements.

To keep the CC personnel blinded to the previous visit's BP measurements, clip a blank *Form 80 – Physical Measurements* to the outside of the participant's file. Leave the *Form 80* attached to the front of the file while you perform and record the BP measurements for the current visit. Once completed, you may then review the contents of the participant's file for BP information relating to the previous visit, if necessary.

9.2.2.2 Arm Circumference Measurement

Since participants have varying body builds, different-sized arm cuffs should be available. Proper cuff size must be used to avoid over- or under-estimation of the correct BP. Measure the participant's right arm to determine the appropriate cuff size before allowing the participant to rest (or the left arm if the right was used for the blood draw). Otherwise, an additional 5-minute rest will be needed before the BP measurement can be taken to ensure accurate readings. If the participant's right arm is injured or missing, use the left arm for the arm circumference and BP measurement.

Use the following procedures to measure the participant's arm circumference to determine the appropriate cuff size:

- Ask the participant to remove her upper garment if she is wearing heavy clothing that covers her arm. (Be sure that the participant is assured of privacy if she must remove clothing.)
- Request the participant to stand with her forearm horizontal to the floor (elbow should be bent slightly).
- Measure her arm length from the bony prominence of the shoulder girdle (acromion) to the tip of the elbow using a tape measure.
- Mark the midpoint on the dorsal (back) surface of the arm.
- Ask the participant to relax her arm along the side of her body.
- Draw the tape measure horizontally around the arm at the midpoint mark, but do not indent the skin.
- Use the measurement to determine the correct cuff size and record the type of cuff and which arm is used on *Form 80*.

Do not use the markings on the BP cuff for reference. Instead, use the following criteria for determining the appropriate cuff size (i.e., size of the cuff's bladder width, not its length).

Arm Circumference (cm/in.)	Cuff's Bladder Size (cm)*
16.0 - 22.5 cm (6.4 - 9 in.)	small cuff (9.0 cm)
22.6 - 30.0 cm (9.1 - 12 in.)	regular cuff (12.0 cm)
30.1 - 37.5 cm (12.1 - 15 in.)	large cuff (15.0 cm)
37.6 - 43.7 cm (15.1 - 17.5 in.)	thigh cuff (17.5 cm)

Keep the above chart of arm circumference measurements and corresponding cuff sizes readily available for easy reference.

9.2.2.3 Rest Period

If the BP is not measured immediately after the pulse measurement, ask the participant to sit with both feet flat on the floor and to rest without talking for five minutes before measuring her BP. Instruct the participant on correct posture with her back supported, both feet flat on the floor, and arm resting on a table next to the chair. The BP measurement area should be free of excessive noise and the participant should not be interviewed at this time.

9.2.2.4 Application of the Cuff

Use the following procedures when applying the BP cuff:

- Ensure that the participant is seated comfortably and both feet are flat on the floor with her sleeve rolled up or her upper garment removed, if necessary.
- Place the appropriate-sized cuff (see *Section 9.2.2.2 - Arm Circumference Measurement*) around the upper right arm (or left, if the right arm is injured or missing) approximately at heart level. Place the participant's palm facing upward (the participant may rest her forearm and elbow on a table). Place the lower edge of the cuff with its tubing connections about one inch above the natural crease across the inner aspect of her elbow.
- Wrap the cuff snugly about the arm, with the inflatable inner bladder centered over the area of the brachial artery. The brachial artery is usually found at the crease of the arm, slightly toward the body. Secure the wrapped cuff firmly by applying pressure to the locking fabric fastener over the area where it overlaps the cuff.

*The bladder widths shown are 40% or more of the corresponding arm circumferences.

9.2.2.5 Determining the Maximal Inflation Level

Determine the pressure to which to inflate the cuff for the systolic BP measurement. This procedure ensures that the cuff pressure at the start of the reading exceeds the systolic BP and allows you to hear the first Korotkoff sound. The procedures for determining the maximal inflation level are as follows:

- Attach the cuff tubing to the conventional mercury sphygmomanometer.
- Palpate the radial pulse (if the radial pulse is difficult to palpate, the brachial pulse may be used).
- Inflate the cuff until the radial pulse is no longer felt (palpated systolic).
- Deflate the cuff quickly and completely.
- Inflate the cuff to 30 mmHg above the palpated systolic pressure (maximal inflation level) for subsequent readings.

9.2.2.6 Performing the Measurement

Wait 30 seconds after determining the maximal inflation level and follow the steps below for performing the BP measurement:

- Place the ear pieces of the stethoscope, with the tips turned forward, into your ears.
- Apply the bell of the stethoscope over the brachial artery with light pressure, ensuring skin contact at all points. (Use of the bell is required because the Korotkoff sounds can be heard more easily.) Effective use of the bell requires careful palpation of the brachial artery to know exactly where to place the bell. Place the bell just below, but not touching, the cuff or tubing.
- Close the thumb valve and squeeze the bulb, inflating the cuff at a rapid but smooth and continuous rate to the maximal inflation level. *Note*: Your eyes should be level with the mid-range of the manometer scale and focused on the level to which you will raise the pressure.
- Open the thumb valve very slightly and maintain a constant rate of deflation of no more than 2-3 mm Hg per second, allowing the cuff to deflate. Listen throughout the entire range of deflation, from the maximum pressure past the systolic reading (the pressure where the first regular sound is heard) until 10 mmHg below the level of the diastolic reading (i.e., 10 mmHg below the level where you hear the last regular sound). (See *Section 9.2.3 - Criteria for Systolic and Diastolic Blood Pressure* and *Section 9.2.4 - Guidelines for Blood Pressure Readings*).
- Deflate the cuff fully by opening the thumb valve and remove the stethoscope ear pieces.
- Record the systolic and diastolic values from the first reading on *Form 80 - Physical Measurements*.
- Hold the participant's arm vertically above her head for a full five seconds to relieve blood pooling.
- Have the participant sit quietly for 30 seconds, then repeat the BP measurement and record the systolic and diastolic values from the second reading on *Form 80 - Physical Measurements*.
- Tell the participant her BP measurement.

9.2.3 Criteria for Systolic and Diastolic Blood Pressure

To identify correctly systolic (Phase I) and diastolic (Phase V) Korotkoff values, listen carefully via the stethoscope while reading and interpreting the mercury column.

- The systolic value (Phase I) is the pressure level at which you hear the first of two or more knocking sounds in appropriate rhythm. *Note:* A single sound heard in isolation (i.e., not in rhythmic sequence) before the first of the rhythmic sounds (systolic) does not alter the interpretation of the BP.
- The diastolic value (Phase V) is the pressure level at which you hear the last of these rhythmic sounds (usually muffled).

- Drop the mercury column at 2-3 mmHg per second, from the maximum inflation pressure until 10 mmHg below that of the last regular sound heard. The control of the deflation rate is essential for accurate readings and depends on proper handling of the bulb and its control valve.

9.2.4 Guidelines for Blood Pressure Readings

- Make all readings to the nearest even digit, rounding up (i.e., read any value that appears to fall exactly between markings on the mercury column to the next higher even-numbered marking).
- Make readings at the top of the meniscus (rounded surface) of the mercury column.
- When the pressure is released too quickly from a high level, a vacuum is formed above the mercury and the meniscus is distorted. Allow a few moments for it to reappear before reading the manometer or do a repeat measurement.

9.2.5 Maintenance of Sphygmomanometer

Check the sphygmomanometer with each use for correct zero. Place the instrument flat on the table and disconnect the inflation system. With eyes level with the zero line, ensure the top of the meniscus is on the zero line. Send the instrument for repair if the reading is either above or below the zero mark.

Check the sphygmomanometer annually to ensure that the cap of the manometer fits properly and tightly. Roll the cuff around a plastic bottle or tin can and secure in place. Close the valve on the air-flo system and inflate the instrument until the mercury rises to 240 mmHg. Close the valve. The mercury column should remain stable. If the column continues to fall, there is an air leak and the system should be re-inflated until the column rises to 200 mmHg. Pinch the tubing at various locations to localize the area of the leak, then replace the leaking tubing, cuff, or valve.

With time, the mercury will become dirty and an oxide layer will be deposited on the inside of the glass tube. Do not attempt to clean the glass column with a pipe cleaner, as hazardous levels of mercury aerosol will be produced. Send the instrument to your local supplier annually for inspection and cleaning or as-needed in the interim.

Since mercury is a hazardous, toxic substance, all maintenance and disposal procedures must be performed carefully and properly (consult your local institution for guidelines). Do not perform any maintenance procedures that will expose the mercury to air. A manometer specialist with expertise in handling toxic substances should be contacted to add or withdraw mercury from the instrument.

With each use, check the BP cuffs to ensure they are in good condition, (i.e., they are not frayed or torn). Also, check the BP cuffs on a regular basis to ensure all sizes of cuffs are available. Document all BP equipment checks on a CC Equipment Log. (See *Volume 7, Section 4, Table 4.1 – CC Equipment Maintenance* for schedule.)

9.2.6 Alert Values

An abnormal BP reading may temporarily exclude a participant from further screening or may prompt referral to her physician. Follow these guidelines for BP alerts:

- Report to the participant's primary care provider (participant remains eligible):

  systolic BP > 160 and < 200, or
  diastolic BP > 95 and < 105

- Make an urgent referral to the participant's primary care provider (within the week) and temporarily exclude from the CT:

  systolic BP > 200 and ≤ 210, or
  diastolic BP > 105 and ≤ 120

- Make an immediate referral to the participant's primary physician via telephone before the participant leaves the CC (with a follow-up letter documenting the information discussed by phone) and temporarily exclude from the CT:

  systolic BP > 210, or
  diastolic BP > 120

Participants may be eligible after starting treatment for hypertension, but repeat readings while on treatment must show systolic BP < 200 and diastolic BP < 105. If a participant seeks treatment after Screening Visit 1 (SV1) and wishes to continue in the study, she may return for Screening Visit 2 (SV2), and should have her BP rechecked at that time. Record the two new BP readings on a new *Form 80 - Physical Measurements*.

9.3 Height (Required)

Clinical Trial and OS participants have their height measured during screening and follow-up visits as outlined in *Vol. 1 - Study Protocol and Policies, Table 1-A1.1 - Frequency of Data Collection*. Clinical Centers are required to use a wall-mounted stadiometer that measures in centimeters (see *Section 2.3.2 - Equipment and Supplies CCs Must Purchase*) for all height measurements. Bone density sites are required to use wall-mounted Harpenden stadiometers for height measurements. The loss of height associated with vertebral deformity is a secondary endpoint of the trial. This objective requires that we achieve the greatest possible precision for this measurement.

9.3.1 Training and Certification

Women's Health Initiative CC staff can perform the height measurement after completion of the WHI training and certification process.

9.3.2 Performing the Measurement

A participant's standing height is the distance from the soles of the feet to the top of the head with the participant standing erect and looking straight ahead. Use the following procedures in determining the participant's height:

- Mount the stadiometer so that the participant stands on a level, uncarpeted, hard surface (or on a piece of plywood on a flat carpet).
- Instruct the participant to remove her shoes.
- Ask her to stand erect with:
  1) her back to the wall-mounted stadiometer,
  2) the back of her head, back (scapulae), and buttocks touching the measuring board, and
  3) with her weight distributed evenly across both feet and her feet flat on the floor with both heels together.
- Check that the participant is in the correct position. (If she is obese or has a kyphotic posture, she may be positioned so that only the buttocks or the scapulae are in contact with the measuring board; in the case of extreme kyphosis, measure the height with the participant standing in a sideways position.)
- Instruct her to look straight ahead and keep her arms relaxed and hanging loosely at her sides.
- Bring the sliding headpiece down firmly, but not tightly, on the top of her head.
- Use a foot stool to adjust the sliding headpiece if the participant is tall, so that your eyes are level with the point of measurement.
- Instruct the participant to inhale deeply and record the reading on the stadiometer just before she exhales.
- Record the height on *Form 80 - Physical Measurements* in centimeters, rounding up to the nearest tenth of a centimeter.
- Tell the participant her height in inches (a chart converting centimeters to inches may be used).

9.3.3 Maintenance of Wall-Mounted Stadiometer

Ensure that the stadiometer is mounted on a straight wall that is at a true 90-degree angle to a level floor. There should be a foot of unoccupied wall space on either side of the stadiometer Whenever the stadiometer is moved, check to confirm that it is positioned properly.

Stadiometer at Non-Bone Density Sites

Check the wall-mounted measuring board annually with a measuring stick to ensure its accuracy. If the measuring board is inaccurate, check the manufacturer's information for instructions on re-mounting.

Regularly clean the surface of the measuring board with mild soap and a damp cloth. Remove the soap with a clean, damp cloth and dry the surface thoroughly. Preserve the board's finish by occasionally treating it with a light furniture wax. Clean the sliding headpiece with a mild glass cleaning solution and a paper towel or dry cloth.

When the stadiometer is not in use, move the sliding headpiece to the bottom of the board so that it rests on the rubber spacers. This will guard against the headpiece sliding down the measuring board on its own and possibly breaking. Alternatively, you may choose to remove the sliding headpiece and place it out of reach. The following is a list of possible problems that may occur with the sliding headpiece and the appropriate adjustments to make:

- Sliding headpiece does not glide freely because it rubs against the wall: slightly loosen the screws from the wall.
- Sliding headpiece is difficult to slide because of pressure between the side of the measuring board and the spring on the inner curve of the sliding headpiece: remove the headpiece and slightly flatten the spring on its inner curve.
- Sliding headpiece is so loose that it falls down the measuring board: remove the headpiece and slightly bend the spring on its inner curve to increase the pressure between the headpiece and the measuring board.

Stadiometer at Bone Density Sites

The Harpenden stadiometer, used to measure height at the bone density sites, contains a direct-reading counter mounted on a counter-balanced carriage that rides on ball bearings. The counter is a self-contained unit and requires no maintenance. A spare counter is often provided for replacements. It is recommended that you place a weight of about 0.5 kg on the headboard to standardize pressure on the head and improve measurement performance.

Because the counter may break if the headboard is "raced" up or down the measuring board, move the Harpenden headboard to its top-most position when not in use. Lubricate any bearings or counter-weight pulleys semi-annually with one drop of light machine or instrument oil. Wash the formica or plastic covering with soap and water.

Daily calibration is required for the Harpenden stadiometer at bone density sites:

- Place a 600 mm metal rod between the headboard and the floor so that it stands vertically.
- If the counter does not record the correct length of the rod, loosen the counter by undoing the two metal retaining screws and pull it away from the main fiber cog of the carriage.
- In this position, turn the small metal cog of the counter until it records the true length of the metal rod.
- Press the counter against the back plate so that the teeth of the counter cog and the carriage cog engage and tighten the retaining screws.
- Move the headboard up and down the backboard a number of times to ensure the counter continues to give an accurate reading. If it does not, the counter must be replaced.

Document, as appropriate, annual or daily stadiometer checks on a CC Equipment Log. (See *Volume 7, Section 4, Table 4.1 – CC Equipment Maintenance* for schedule.)

9.3.4 Reliability Testing of Portable Stadiometer

Clinical Centers are required to use a wall-mounted stadiometer that measures in centimeters for all height measurements. Clinical Trial and OS participants may have height measurements made using a portable stadiometer during screening and follow-up visits at WHI off-site clinic visits. However, a CC must obtain approval from the CCC before using a portable stadiometer. To obtain approval, the CC must document the reliability testing and provide the CCC with a copy of the results.

Reliability testing will help to assure the quality of the height measurement using the portable stadiometer both study-wide and by individual clinic staff. Reliability testing will also serve to collect information on the reliability of height measurements using wall-mounted stadiometers compared to portable stadiometers.

The reliability testing requires two examiners at the CC to do height measurements using a wall-mounted stadiometer and a portable stadiometer. Height measurements must be done for six participants. To compare the effect between the examiner and the stadiometer, both examiners will take the participant's height measurement using the wall-mounted stadiometer. One examiner will assemble the portable stadiometer and perform the measurement procedure without reading the measurement. The other examiner will read and document the results of the height measurement using the portable stadiometer. The portable stadiometer must be disassembled and re-assembled between each reading, with each examiner assembing and taking the reading three times. Record the results on the Portable Stadiometer Reliability Testing log and forward to the CCC (see Figure 9.2). The CCC will notify the CC on results of the testing. Refer to Bulletin 86 text or WHI Directory for the recommended distributor.

Performing the Measurement

Two examiners (#A and #B) will validate the data for the portable stadiometer reliability testing using the procedure below. To minimize any possibility of bias, both examiners must be blinded to each other's measurements.

- Explain the procedure to the participant and why it's being done.
- Examiner #A will measure a participant's height using the wall-mounted stadiometer in accordance with the standard WHI procedure outlined in Section 9.3.2 - Performing the Measurement.
- Examiner #B will repeat this procedure 15-30 minutes later using the same wall-mounted stadiometer for the same participant.
- Examiner #A will disassemble and reassemble the portable stadiometer and perform the measurement procedure according to the manufacturer's recommendations.
- Examiner #B will read and record the height measurement results from the portable stadiometer.

  Note that each examiner must disassemble and re-assemble the portable stadiometer, prepare participants for the height measurement, and read and record the height measurement using the portable stadiometer for three participants (total of 6 participants at each CC).
- To preserve the integrity of the reliability testing, do not give the participant the measurements until after all three measurements (2 wall-mounted and 1 portable) are taken.

Completion of Reliability Testing Log

Record the data for the three measurements for each participant (two for the wall-mounted stadiometer reading and one for the portable stadiometer reading) on a CC copy of *Figure 9.2 – Portable Stadiometer Testing Log* along with the appropriate examiner IDs for each measurement. Once the six participant height measurements are completed, send the original log to your CM liaison at the CCC.

The CCC will review the completed Reliability Testing Log. Once approved, the CCC will forward approval for local use of the portable stadiometer to the CC.

Figure 9.2

Portable Stadiometer Reliability Testing Log

(not for key-entry)

Clinical Center:

Date	CC/Participant ID	Wall-Mounted Stadiometer				Portable Measuring Board	
		ID# of Examiner A	Height	ID# of Examiner B	Height	ID# (of examiner who reads and records portable measurement *)	Height
1. __/__/__	__ __ - __ __ __ __ __ - __	__ __ __	_____.___cm	__ __ __	_____.___cm	__ __ __	_____.___cm
2. __/__/__	__ __ - __ __ __ __ __ - __	__ __ __	_____.___cm	__ __ __	_____.___cm	__ __ __	_____.___cm
3. __/__/__	__ __ - __ __ __ __ __ - __	__ __ __	_____.___cm	__ __ __	_____.___cm	__ __ __	_____.___cm
4. __/__/__	__ __ - __ __ __ __ __ - __	__ __ __	_____.___cm	__ __ __	_____.___cm	__ __ __	_____.___cm
5. __/__/__	__ __ - __ __ __ __ __ - __	__ __ __	_____.___cm	__ __ __	_____.___cm	__ __ __	_____.___cm
6. __/__/__	__ __ - __ __ __ __ __ - __	__ __ __	_____.___cm	__ __ __	_____.___cm	__ __ __	_____.___cm

Complete and forward original log to your CCC CM Liaison (keep a copy at your CC).

*Note: Other examiner (A or B as appropriate) will disassemble and reassemble the portable stadiometer and perform measurement procedure (without reading the measurement).

9.4 Weight (Required)

Clinical Trial and OS participants have their weight measured during screening and follow-up visits as outlined in *Vol. 1 - Study Protocol and Policies, Table 1-A1.1 - Frequency of Data Collection*. A balance beam scale that measures in kilograms is required for all weight measurements (see *Section 2.3.2 - Equipment and Supplies* CCs Must Purchase).

9.4.1 Training and Certification

A WHI staff person may measure body weight after completion of the WHI training and certification process.

9.4.2 Performing the Measurement

Use the following procedures to measure a participant's weight:

- Instruct the participant to remove her jacket, her shoes, other heavy clothing, and to empty her pockets.
- Lift both poises (weights) and position them at zero before asking the participant to step onto the scale. Ensure that the beam is balanced evenly at zero with no weight on the scale (see *Section 9.4.4 - Calibration Check* for recalibration guidelines).
  Ask the participant to step onto the scale, facing the measurement beam.
- Instruct her to stand in the middle of the platform on the scale with her head erect and eyes looking straight ahead.
- Ask the participant to distribute her weight evenly on both feet.
- Lift the counterweight (larger weight), and slide it to the right until the beam approaches balance with the participant standing in the proper position.
- Adjust the top poise until the beam is balanced evenly.
- Read the weight with your eyes level to the point of measurement on the scale.
- Ask the participant to step off the scale.
- Record the weight on *Form 80 - Physical Measurements*, rounding up to the nearest tenth of a kilogram.
- Return the counter poise to the 40-kg mark and the top poise to zero.
- Tell the participant her weight in pounds (a chart converting kilograms to pounds may be used).

9.4.3 Maintenance of Scale

With normal use, the scale should last for many years. In order to ensure long life, the following maintenance practices are recommended:

- The scale equipment should remain in a stationary position; it should not be moved from room to room, nor moved within the same room.
- The scale should not be tipped, and the platform should be kept free of objects.
- The scale should always remain standing on a level, uncarpeted, hard surface or on a piece of plywood on a flat carpet.
- While the top poise slides easily across the column, the counter poise must always be lifted carefully before it is moved across the column. This procedure prevents wear on the notches, which could cause incorrect readings.
- The top poise should rest on zero when the scale is not in use. The counter poise should rest on the 40-kg mark when the scale is not in use. If the counter poise is left at zero, the gear mechanisms may be subjected to unnecessary wear.

9.4.4 Calibration Check

Before you begin using the balance beam scale and annually thereafter, have the scale certified by a local department of weights and measures or a certified scale technician. If this certification is not possible, inform the Clinical Coordinating Center (CCC).

Check the scale against known weights on a semi-annual basis and whenever the scale is moved, using the procedure below. Each CC should have a 50-kg weight (or two 25-kg weights) for this purpose. If these weights are not certified (e.g., body-building weights), have their exact weight determined by the local department of weights and measures or a certified scale technician. Perform the calibration check as follows:

- Put both the top and counter poises in the zero position. With no weight on the platform, the beam should "float."
- If the beam is not balanced when both poises are in the zero position, turn the balance screw to the right or left until the scale is balanced.
- Put the known weights on the scale, and adjust the poises until the beam "floats" and verify that the scale is measuring the weights accurately.
- If the scale is outside a 0.2 kg range of accuracy, call an independent service technician to recalibrate it.

Document semi-annual scale checks and annual certifications on a CC Equipment Log. (See *Volume 7, Section 4, Table 4.1 – CC Equipment Maintenance* for schedule.)

9.4.5 Portable Scales

Often times a CC will use a portable scale (not a balance beam scale) to measure weight if clinic operations are performed at a remote site. If the CC plans to use a portable scale, the CC must send the CCC specifications of the name, model number, and the local calibration services available. The CCC must approve any non-WHI equipment changes.

Criteria for a portable scale include the following:

- Scale is well-made and sturdy
- Scale must be able to be calibrated
- Scale weighs in kilograms
- Scale can measure weights up to at least 160-180 kilograms (350-400 pounds)
- Allowable scale error is within 1 kg of certified weights
- An independent certified technician certifies portable scale annually

Equipment checks and procedures include the following:

- Calibrate the scale with two 25 kg weights and one 150 kg weight semi-annually.
- Document annual and semi-annual certifications and calibrations, respectively, in an equipment log.
- Set the scale to zero before weighing participants.
- If scale operates on batteries, use a power cord in lieu batteries.

9.5 Waist and Hip Circumference (Required)

Clinical Trial and OS participants have their waist and hip circumference measured during screening and at specified follow-up visits (CT in year 1 and a subsample of CT in years 3, 6, and 9; OS in year 3) and at close-out as outlined in *Vol. 1 - Study Protocol and Policies, Table 1-A1.1 - Frequency of Data Collection*. A measuring tape that measures in centimeters is required for this procedure and the CCC provides tape measures in two lengths: 152 cm (5 ft.) and 183 cm (6 ft).

9.5.1 Training and Certification

Women's Health Initiative CC staff can perform waist and hip circumference measurements after completing the WHI training and certification process.

9.5.2 Performing the Measurement (Waist Circumference)

- Instruct the participant to remove any extra layers of clothing, belts, girdles, or binding pantyhose (only non-binding undergarments can be worn).
- Instruct the participant to stand with her weight distributed evenly on both feet, abdomen relaxed, arms at her sides, and feet together.
- Facing the participant, place the tape measure in a horizontal plane at the level of the natural waist, which is the narrowest part of the torso. An assistant may be needed to help position the tape in a horizontal plane. Alternatively, a wall-mounted mirror can be used to assist with positioning the tape in the horizontal position. If it is difficult to identify a waist narrowing, measure the smallest horizontal circumference in the area between the participant's ribs and iliac crest.
- Ensure that the zero end of the tape is below the measurement value.
- Verify that the participant is standing erect and that the tape measure is horizontal.
- Take the waist measurement at the end of a normal expiration, without the tape measure compressing the skin.
- Record the waist measurement on *Form 80 - Physical Measurements*, rounding up to the nearest half centimeter.

9.5.3 Performing the Measurement (Hip Circumference)

- Measure the hip circumference after the waist circumference.
- Place the tape measure around the participant's hips in a horizontal plane at the site of maximum extension of the buttocks.
- Ensure that the zero end of the tape is below the measurement value.
- Ensure that the tape measure is in contact with, but does not compress, the participant's skin.
- Verify that the participant is standing erect and that the tape measure is horizontal. An assistant may be needed to help position the tape in a horizontal plane. Alternatively, a wall-mounted mirror may be used to ensure that the tape is positioned in a horizontal plane if an assistant is unavailable.
- Record the hip circumference measurement on *Form 80 - Physical Measurements*, rounding up to the nearest half centimeter.

9.5.4 Maintenance of Measurement Tool

Inspect the tape measure monthly, as needed, for damage or wear and tear. Document tape measure checks on an Equipment Log (See *Volume 7, Section 4, Table 4.1 – CC Equipment Maintenance* for schedule.) Contact the CCC for a replacement, as needed.

9.6 Functional Measurement (Subsample Only) Status

A subsample of CT participants (identified by WHILMA) who are 65 to 79 years old at baseline will have functional status measurements performed during screening and follow-up visits, as outlined in *Vol. 1 - Study Protocol and Policies, Table 1-A1.1 - Frequency of Data Collection*. These measurements will include grip strength, timed chair stands, and a timed walk.

Experience from other studies has suggested that participants have enjoyed the functional status measures and the challenges they present. The value of the physical performance data will be of benefit in understanding the relationship between physical functioning, institutionalization, service utilization, health status, and mortality.

9.6.1 Functional Status Measurement Procedures for Older Women

The following guidelines describe considerations for performing functional status measurements in older women. Refer to *Section 20.2.1 – Older Women* for more guidelines on working with older women.

9.6.1.1 Footwear

Measures of physical functioning should be performed with the participant wearing tennis shoes or shoes with very low or no heels. Some of the tests are much harder to perform with higher heels on. Ask the participant if the footwear she is wearing is what she wears most of the time around the house. Soft-soled, non-heeled slippers should not be worn; they may cause the participant to slip.

9.6.1.2 Physical Limitations and Safety Precautions (Required)

If the participant indicates she has a physical problem, discuss with her whether she should attempt each test, given the physical problem. You might say, "With me standing here beside you, do you think it would be unsafe for you to try to do it?"

Occasionally the participant will be so unsteady that the staff member will be concerned for her safety. If you are uncertain about the safety of performing a particular test, refer the participant to the CP or other appropriate clinician for guidance. The staff member may decide not to perform the test if the participant appears in imminent danger of falling. If a test is not conducted for safety reasons, mark the appropriate response on the form. In all instances, stay close to the participant to offer support. Stay to the side of the participant, rather than in front, to steady her if necessary. After reading the verbal instructions and demonstrating each maneuver for the participant, ask, "*Do you feel it would be safe to try?*"

If there is any reason that either the WHI staff person or the participant feels a particular performance measure would be unsafe, the measure should not be attempted. Emphasize this without alarming the participant.

9.6.1.3 Refused/Unable

If a test is not attempted because the participant refuses or prefers not to complete it, record the reason on *Form 90 - Functional Status*. If a test is attempted but the interviewer or the participant decides that the test cannot be completed, record that the test was not completed.

9.6.1.4 Falls

In the unlikely event that a participant should begin to fall, do not attempt to pull her up, rather help to lower her down gently in order to reduce the impact of the fall. Do not hold the participant by the hand; hold her around the torso under the shoulders. If the participant falls and is not injured, help her up by having her get on her knees or on all fours, place a chair next to her and have her support herself on the chair as you lift under the shoulders. Do not try to lift the participant alone from the floor. It may be helpful to have the stopwatch around your neck or wrist so that you can immediately let go of the stopwatch and have both hands free to help the participant. In the event that the participant requires assistance, simply drop the stopwatch and

disregard the timing. Local incident reports and appropriate medical referrals should be made based on the severity of the fall.

9.6.1.5 Improving Data Quality

Three techniques are recommended to improve data quality:

- *Commitment* – motivate the participant. Getting the participant to state her willingness to try to do the functional status measures and agreeing to work hard is an important first step.
- *Instructions* – should be directive and motivational and should make clear what is to be accomplished and the criteria for a good performance. Instructions include detailed verbal instructions, careful demonstration of each maneuver (with concurrent verbal instructions), asking if the participant understands, and answering any questions she might have. You may need to provide verbal instructions or a demonstration of the maneuver more than once. For some participants, detailed verbal instructions may seem tiresome or unnecessary. It may help to say to each participant that you are going to explain each test in detail because this is the best way to make sure that everyone does the test in the same way. It is up to you to determine whether the participant understands what is required and to provide the appropriate level of instruction.
- *Feedback* – provide cues to the participant about the adequacy of her performance. The feedback should reinforce the instructions and need for commitment. Feedback may include repeating relevant parts of the instructions as well as giving such encouragement as "*Keep going*", "*Good*", "*Steady*", or "*We appreciate your effort*".

9.6.2 Training and Certification

Women's Health Initiative CC staff can perform functional status measurements after completion of the WHI training and certification process.

9.6.3 Grip Strength (Required)

Grip strength is a measure of upper-body strength and has been used as a general indicator of frailty. Measure the grip strength in the dominant arm using an adjustable, hydraulic hand grip dynamometer that measures in kilograms (see *Section 2.3.2 - Equipment and Supplies CCs Must Purchase*).

9.6.3.1 Grip Strength Procedure

Measure the grip strength twice in the dominant arm unless the participant has had a recent flare-up of extreme arthritis, recent surgery, or residual weakness from an injury or stroke. If both arms are affected, do not measure the participant's grip strength.

- Determine whether to test grip strength, and which side to test, by doing the following:
  1. Hand dominance: determine whether the participant is right- or left-handed. In ambidextrous participants, take the measurement on the right side.
  2. Determine if the participant has had a stroke or injury with residual weakness on one or both sides. You could ask, "*Have you had a stroke or injury that has made one arm weaker than the other?*" In participants with a history of injury or stroke with residual arm weakness on the dominant side, take the measurement on the other side. If both sides are affected, do not measure participant's grip strength.
  3. Determine if the participant has had an acute flare-up of arthritis in the hand or surgery on the hand or wrist in the past three months (12 weeks). You could ask, *"Has any pain or arthritis in your hands gotten worse recently? Have you had any operations on your hands or wrists in the past three months?*" If she has had an acute flare-up of arthritis or is less than 13 weeks post-fusion, arthroplasty, tendon repair, or synovectomy (or other related surgeries), then do <u>not</u> test grip

strength on the affected side. If both sides are affected or the participant refuses the procedure, do not test grip strength and document this on *Form 90 - Functional Status*.

- Demonstrate how to do the procedure by placing the dynamometer in your dominant hand with the dial facing away from the palm. It is recommended that you say, "*In this exercise I'm going to use this instrument to measure the strength in your arms. First, let me show you how it's done*." Your arm should be flexed 90 degrees at the elbow with the forearm parallel to the floor. As you demonstrate, instruct the participant to squeeze the handle maximally while simultaneously lowering the arm on a 3-second count. Release the grip when your arm is extended completely, hanging straight at your side. Your arm should not touch your body and the gripping action should be a slow, sustained squeeze rather than an explosive jerk.

- Have the participant practice the maneuver by doing one sub-maximal trial, using her dominant arm, to determine if she understands the procedure. You could say, *"I'd like you to hold the dynamometer in your (right/left) hand and just slightly squeeze the handle like I showed you*." Make sure the participant understands the entire procedure. The hand grip should be at the second setting and the participant should use the wrist safety strap on the dynamometer to minimize any chance of dropping the instrument.

- Reset the dial to zero.

- Have the participant perform two trials on the same side, coaching her to squeeze as hard as she can. You could say, "*Now, when I say 'squeeze,' squeeze as hard as you can while I count to three. The two pieces of metal will not move, but I will be able to read your grip strength on the dial. If you feel any pain, tell me and we will stop.*"

- Reset the dial to zero after each trial. If the participant has trouble completing two trials with her dominant hand, attempt to get two readings with her non-dominant hand. If the participant can only complete one trial, document that measurement on *Form 90 - Functional Status*.

- Record the measurement on the dial to the nearest kilogram (rounding up) for both trials on *Form 90 - Functional Status.*

- Record which hand was used to measure the grip strength.

9.6.3.2 Maintenance of Hand Grip Dynamometer

For routine maintenance, follow the instructions in the dynamometer owner's manual for checking the posts, hydraulics, handle, and peak-hold needle on a semi-annual basis. Be careful not to drop the dynamometer.

Check the zero position of the gauge needle with each use. To adjust it back to zero, unscrew the gauge cover. Using a screwdriver, turn the slot in the gauge needle shaft in the opposite direction that you want the needle to rotate. Restrain the needle from turning by holding it as near the center as possible while turning the shaft. The adjustment is a trial-and-error procedure, so if the needle does not end up at zero after the first try, repeat the procedure. Once the adjustment has been completed, replace the gauge cover.

Check the calibration of the hand grip dynamometer on a semi-annual basis. Hang individual 5-kg and 20-kg (5-kg and 15-kg may be used instead of 20-kg) weights across the handle, using one large (or two smaller) Velcro straps on each side of the dynamometer handle. Lift the weights slowly and just slightly off the floor while they are strapped to the dynamometer handle. To avoid potential for injury, several CC staff people should help with this calibration check. The lifting motion should be very slow and smooth and the weight should remain distributed evenly between the two sides of the handle. Record the maximum kilograms registered on an Equipment Log. Repeat the procedure three times and average the three calibration trials.

The dynamometer should be accurate within ± 2 kg for the average of the three calibration trials. If the calibration check is not within these limits, it may be necessary to send the dynamometer to the manufacturer for repair and recalibration. DO NOT attempt to recalibrate the dynamometer yourself. Calibration errors can be caused by dropping the dynamometer or by leaks in the hydraulic system. The manufacturer may have a

lending program so that CCs will not be without a dynamometer; if not contact the CCC. Note: Clinical Centers are no longer required to send the dynamometer to the manufacturer for routine calibration, only on an as-needed basis.

Document semi-annual hand grip checks and calibrations on a CC Equipment Log. (*See Volume 7, Section 4, Table 4.1 – CC Equipment Maintenance* for schedule.)

9.6.4 Chair Stand (Required)

A participant's performance on the chair stand offers information about her lower body strength and mobility and is a general indicator of frailty. A stopwatch and a standard, straight-backed, flat-seated (non-padded), armless chair is required for this procedure. A thin strip of masking tape should be placed across the seat of the chair half-way between the front and the back of the seat.

9.6.4.1 Chair Stand Procedure

The chair stand performance involves determining the participant's ability to stand up from a standard chair and counting the number of times she arises from the chair in 15 seconds, both without using her arms. The participant should be wearing comfortable shoes (heels less than 1½") or stockings. Perform the chair stand as follows:

- Place the back of the chair against a wall to steady it. Stand next to the participant to provide assistance if she loses her balance.
- Single chair stand:
    1. Have the participant sit in the chair, assuming the position from which she would normally stand up from a chair (but no more than half-way forward on the seat of the chair) with her feet resting on the floor and her arms folded across her chest. Ask her to stand up without using her arms. You could say, "This test measures the strength of your legs. *Fold your arms across your chest. Now please try to stand up without using your arms. If it's painful, you can stop*." If she is unable to rise without using her arms, ask her to stand up using her arms to push off. If she is unable to stand up on her own or refuses to complete the test, thank her for her efforts and do not continue the test. Document this information on *Form 90 - Functional Status*.
    2. Have the participant sit down again.
- If the participant was able to complete one chair stand without using her arms, have her perform the timed chair stand:
    1. Ask her to repeat the chair stand starting from the sitting position and to continue repeating stands for a total of 15 seconds. You could say, "*Please keep your arms folded across your chest. When I say 'Ready, stand!,' Stand up straight and sit down, stand up and sit down, and keep on standing and sitting as fast as you can without stopping in between or using your arms to push off. I want to see how many times you can stand, then sit, stand, then sit in 15 seconds. If you start having pain or discomfort, you can stop the procedure. Now watch while I demonstrate*." Demonstrate two to three rapid chair stands.
    2. Tell the participant to stand ("*Okay, start*!") and start the stopwatch. Count out loud each time she arises. When 15 seconds have passed, immediately stop the stopwatch while you say, "*Okay, stop*."
    3. Record the number of completed chair stands (i.e., the number of times the participant arises before time is called). If she tires before completing 15 seconds, confirm that she cannot continue anymore. If she says she can continue, keep timing; otherwise stop.
    4. Allow the participant to rest quietly for 1 to 2 minutes (or longer, if needed), and repeat the timed procedure.
    5. Record the results of the chair stand on *Form 90 - Functional Status*.

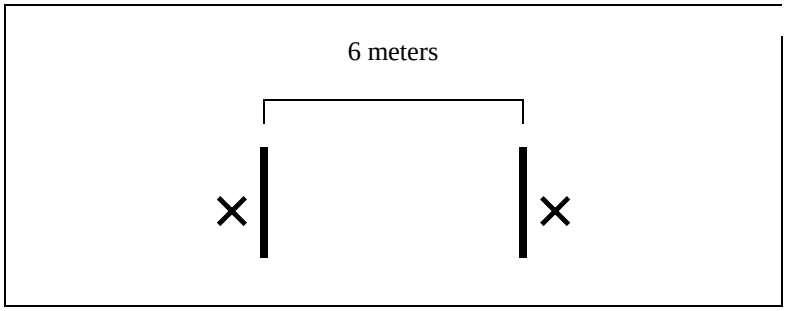
9.6.5 Timed Walk (Required)

The timed walk functional status test measures a participant's functional ability and fitness. A stopwatch and 6-meter gait course (see below) are required for this measurement.

9.6.5.1 Gait Course

Set up a gait course on an uncarpeted or flat-carpeted floor 6 meters in length. Mark the course by lines at either end and by a large, black "X" ½-meter beyond the line at either end (see *Figure 9.1 - Gait Course*).

Figure 9.1
Gait Course



9.6.5.2 Timed Walk Procedure

This performance test measures a participant's ability to perform a 6-meter walk and the time required (in seconds) to complete the walk. Perform this test twice. The participant may use walking aids (such as canes or walkers) during this test. The participant should be wearing comfortable walking shoes. In all instances, the examiner should walk beside and just behind the participant and be ready to support her if she should trip or lose her balance. Occasionally, a participant will be so unsteady on her feet that the examiner will be concerned for her safety. The examiner may decide not to perform the test if the participant appears to be in imminent danger of falling (e.g., someone who arrives in a wheelchair but wants to try every test). (See *Section 9.6.1.2 - Physical Limitations and Safety Precautions*.) As a general rule, each participant should be encouraged to attempt the test. If the participant is too unsteady to perform the test, but tries, indicate this on *Form 90 - Functional Status*.

- Tell the participant that she should walk normally down the length of the course. If she usually uses a cane or other walking aid and would feel more comfortable with it, then she should use it during this test.
- Have the participant stand just behind and in the center of the starting line on the gait course. Explain that this is the walking course and she should walk to the other end of the course at her usual speed, just as if she were walking down the street to go to the store. Instruct her to walk all the way to the "X"-mark at the other end before she stops. Let her know that you will walk with her and keep track of the time it takes her to complete the course. Advise her that if she has pain or feels like she might fall, she can stop at any time.
- When the participant is positioned properly at the start line, instruct her to begin and start the stopwatch at the word, "*Begin*."
- Walk beside and just behind the participant for the entire course.
- Stop the stopwatch when <u>one</u> of the participant's feet is <u>all the way across</u> the end line.
- Have the participant turn around and repeat the test in the opposite direction.
- Record the participant's ability to complete the test, her use of any assistive devices, and the two completion times on *Form 90 - Functional Status*.

9.7 Clinical Breast Exam (Required)

Clinical Trial participants will have a Clinical Breast Exam (CBE) during screening and annual follow-up visits as outlined in *Vol. 1 - Study Protocol and Policies, Table 1-A1.1 - Frequency of Data Collection* and at non-routine visits if clinically indicated. The CBE is optional for Dietary Modification (DM) participants who have signed the appropriate consent form (i.e., that indicates a CBE may be done).

If a participant refuses to have the CBE done at the CC, a written report of an outside provider exam should be obtained and abstracted onto *Form 84 – Clinical Breast Exam*. If the written report cannot be obtained, a verbal report from a clinician (i.e., LPN, RN, PA, NP, or MD) is acceptable. A report of normal is acceptable. Any abnormal reports need to be thoroughly investigated and documented.

9.7.1 Training and Certification

A WHI physician, licensed practical nurse (LPN; trained and supervised in accordance with state practice regulations), registered nurse (RN), nurse practitioner (NP), or physician assistant (PA) may perform a CBE after completion of the WHI training and certification process.

9.7.2 Performing the CBE

Perform the CBE in a private examining room with good lighting (the CBE can be performed just before the pelvic exam for HRT participants or in conjunction with the electrocardiogram (ECG) if done at a different screening visit). For this exam, have the participant remove her upper clothing, including her bra, and have her put on a front-opening gown.

- Inspect the breasts first with the participant in a relaxed sitting position, then with arms overhead, then with her hands pressed against her hips, and finally, leaning forward.
- Inspect each breast for asymmetry, skin dimpling, or nipple retraction.
- Palpate the axillae for lymph nodes.
- Have the participant lie in a supine position and ask her to place her left hand under her head while a small pillow is placed under her back on the same side.
- Palpate the left breast systematically from the outer to inner edge of each quadrant so as to cover all quadrants, or in decreasing concentric circles.
- With her arm by her side, again palpate the axilla for lymph nodes.
- Repeat the procedure on the right side.
- Enter the findings of the CBE on *Form 84 - Clinical Breast Exam*.
- Document any abnormalities that require follow-up evaluation and record follow-up results on *Form 84*.
- See *Section 5.1.2.1 - Exclusions Based on Baseline Clinical Breast Exam Findings for CT* eligibility guidelines.

9.8 Breast Self-Exam Instruction (Required)

Clinical Trial participants have breast self-examination (BSE) teaching during one of their screening visits. The BSE teaching can be done during the CBE and should take no more than 10 minutes. Breast self-examination practice may be reinforced with a shower card or video during subsequent follow-up visits (if needed) and re-instruction may be offered (if needed).

9.8.1 Training and Certification

A WHI physician, LPN (trained and supervised in accordance with state practice regulations), RN, NP, or PA may teach BSE after completion of the WHI training and certification process.

9.8.2 Performing Breast Self-Exam (BSE) Instruction

Ask the participant if she knows how to do BSE and, if so, ask her to demonstrate her BSE method.

If she is uncomfortable demonstrating BSE, or if further instruction is necessary, begin with a brief review of the anatomy of the breast, using the breast model (supplied by the CCC) as a visual aid. Include explanations of topography, general appearance and shape, and normal variability of breast tissue consistency. Describe the different types of breast tissue and how they may feel to palpation. This review may be done by showing a BSE video (an annotated listing of available videos can be obtained from the CCC). Help the participant identify a date and time each month when it is convenient for her to perform the BSE.

Using the breast models or the participant's own breasts, demonstrate a decreasing concentric circular or quadrant palpation technique starting at the upper outer edge of the breast. A teaching model that has soft, nodular background tissue with variably-sized simulated tumors can also be used. Throughout this demonstration, emphasize the importance of proper palpation technique using your finger pads in a massaging motion with firm pressure. You can ask the participant to palpate the practice model.

Describe to the participant how to inspect her breasts in a relaxed sitting or standing position in front of a mirror. Show her how to perform BSE on herself by having her lie supine in the same position as for the CBE. Tell her that she should do these maneuvers while lying down or standing in the shower. Holding your fingers over hers, move her hand in a circular motion over her breast to teach her the appropriate palpation technique. Watch her palpate her entire breast. Watch her abduct one arm completely and palpate her axilla with her opposite hand. Teach and watch the examination of both breasts and axillae.

Mark on *Form 84 - CBE* when the BSE is completed.

Note: The BSE may be streamlined for participants who demonstrate correct BSE (e.g., it may not be necessary to watch the video or use the breast models). BSE teaching is not a WHI intervention, but is an ethical consideration that should be available as part of the overall baseline breast health evaluation for CT participants.

9.9 Pelvic Exam and Pap Smear

All HRT participants have a pelvic exam during screening. Pap smears should also be done at the time of the screening pelvic exam, unless the participant has had a Pap smear in the last 12 months, in which case a report of the findings can be requested. Hormone Replacement Therapy participants with intact uteri will have follow-up pelvic exams, and HRT participants with intact cervices will have Pap smears, as outlined in *Vol. 1 - Study Protocol and Policies, Table 1-A1.1 - Frequency of Data Collection*.

As of July 9, 2002, E-plus-P participants are no longer required to have annual pelvic exams and pap smears every three years. It is recommended that CCs consider this change on an individual basis with these participants, since some participants may still desire an examination, particularly if they do not have a current outside care provider. If the participant elects to have her examinations with her outside provider, clinics are no longer required to obtain documentation for these exams. It is recommended that if an exam is completed in the clinic, the appropriate form be completed (*Form 81 – Pelvic Exam* and/or *Form 92 – Pap Smear*).

E-Alone participants are still required to have a pap smear every three years if their cervix is still intact and a *Form 92 – Pap Smear* should be completed. If the participant refuses to have the pap smear in the clinic, a written or verbal report from the outside provider is required.

9.9.1 Training and Certification

A WHI CC physician, RN (trained in accordance with state regulations), NP, or PA may perform the pelvic exam and Pap smear after completion of the WHI training and certification process. Clinical Center staff performing these procedures must also be licensed appropriately in the state where the CC is located and comply with all state and federal regulations regarding physician supervision of their clinical practice, if appropriate.

9.9.2 Performing the Pelvic Exam and the Pap Smear

Perform the pelvic exam in a private examination room with good lighting. A female assistant may remain in the room if appropriate. Proper hand washing and clean technique must be used. Ask the participant to empty her bladder before the exam and be sure that she is gowned and draped appropriately during the exam.

Assist the participant into the lithotomy position, placing her feet in the stirrups at a comfortable length to prevent excessive abduction of the hips. The participant's hands should be either at her sides or over her chest to enhance abdominal muscle relaxation. With gloved hands, inspect the external vulva and perineum. Ask the participant to perform a valsalva maneuver (forcible exhalation against a closed glottis) to evaluate the pelvic structures for prolapse and relaxation. Then, insert a speculum that is lubricated with warm water and/or a small amount of water-soluble lubricant. Choose the appropriate-sized speculum; many older participants will require small specula. Inspect the vaginal mucosa and cervix. In participants with an intact cervix, obtain a cervical scraping from the exocervix using a wooden spatula first and then obtain an endocervical sample with the cytobrush. Two slides or one slide with two smears should be prepared—one smear marked "endocervical" and the other marked "exocervical." It is necessary that vaginal or cervical cells be collected and that an attempt be made to collect endocervical cells if the cervix is present. For the baseline exam, participants without a cervix should have a Pap smear scraping taken from the apex of the vagina. Only one slide need be prepared for such participants, marked "vaginal cuff." Immediately spray smeared slides with a fixative or place in a fixative jar to prevent air-drying artifact. Finally, remove the speculum and with lubricated gloved hands (e.g., K-Y jelly), perform a bimanual exam. Palpate for uterine size, consistency, position, mobility, and tenderness, as well as the presence of uterine or adnexal masses and uterine fibroids. Ask the participant to perform a valsalva maneuver to evaluate the presence of cystocele, rectocele, or uterine prolapse. A recto-vaginal exam should be done to assess a posterior uterus. Indicate results of the pelvic exam on *Form 81 - Pelvic Exam*.

Label the Pap smear slides with the participant's barcode labels and send to the local laboratory within two days of the procedure. Record the results on *Form 92 - Pap Smear*.

It is possible for a participant to have a cervix and not a uterus. These participants will have undergone a subtotal hysterectomy. Some participants may know that they had a "partial" hysterectomy, or they may not be aware that the cervix remains. If you see a cervix in a participant who gives a history of hysterectomy, request a copy of the operation records. If only a cervix is present, the participant should have baseline and follow-up Pap smears as for participants who have not had a hysterectomy. *See Sections 5.1.2.2 - Exclusions Based on Baseline Pelvic Exam Findings* and *5.1.2.3 - Exclusions Based on Baseline Pap Smear Findings* for further guidelines.

In the rare event that a uterus or uterine tissue is "discovered" in a participant who previously reported having a hysterectomy, contact your CCC Data Coordinator Liaison before dispensing any HRT study pills. The participant will be switched in WHILMA to the appropriate HRT study pills (either PERT or PERT placebo). Present the case to the CC consulting gynecologist, who will decide if an endometrial biopsy is necessary. Manage the participant accordingly.

9.9.3 Pelvic Exam and Pap Smear Findings

Follow usual clinical practice related to pelvic exams and Pap smear findings.

If endometrial cells or AGCUS (atypical glandular cells of undetermined significance) are found on Pap, the participant must have an EA and be referred to her primary care provider for cervical evaluation (e.g., colposcopy). The EA may be done at either the CC or by her primary care provider. If an EA is necessary, continue or discontinue study pills based on the algorithms in *Volume 2, Section 5.4.3.2 – Management According to Endometrial Histology.*

A participant with ASCUS (atypical squamous cells of undetermined significance) on Pap must have a repeat Pap. The repeat Pap may be done at the CC or by the participant's primary care provider. The participant's primary care provider may choose to do some other cervical evaluation (e.g., colposcoy) rather than a repeat Pap. Refer any participant with an abnormal repeat Pap to her primary care provider for further cervical evaluation (e.g., colposcopy).

Document the cervical follow-up to the initial Pap smear (e.g., 2nd Pap, colposcopy, biopsy) in the follow-up section of *Form 92 – Pap Smear*. Document any endometrial evaluation on *Form 82 – Endometrial Evaluation* or *Form 83 – Transvaginal Uterine Ultrasound* as appropriate.

(AGCUS and ASCUS categories as well as place to record results of second Pap will be included in *Form 92 – Pap Smear*, Ver. 2, scheduled for release with WHILMA V.43 upgrade in January 2001.)

9.10 Endometrial Aspiration

As of July 9, 2002, Endometrial Aspirations are no longer required for the subsample group.

Hormone Replacement Therapy participants with uteri will have endometrial aspirations during screening (before randomization) and, depending on subsampling and symptoms at routine visits and unscheduled follow-up contacts (see *Vol. 1 - Study Protocol and Policies, Table 1-A1.1 - Frequency of Collection*). A pathology report of an outside endometrial aspiration can be requested to document a baseline (if performed in the previous 12 months), routine or non-routine follow-up endometrial aspiration. Provide the participant with the HRT Handbook (see *Vol. 2, Appendix F, Figure F.3.2*), point out the relevant sections, and answer any questions she might have about the procedure and post-procedure care. Although it is possible for a participant to have a cervix and not a uterus, only those participants with uteri will have endometrial aspirations. If the practitioner cannot palpate a uterus, but the participant says she has not had a hysterectomy and a cervix is present, then it is safe to proceed with the endometrial aspiration. Occasionally, a short segment of lower uterine segment with functional endometrial tissue will be inadvertently left in situ during a subtotal hysterectomy. This should be suspected if the participant has had a subtotal hysterectomy and reports intermittent vaginal bleeding after the hysterectomy. Consult the CC Consulting Gynecologist in this case to determine if endometrial sampling should be attempted.

9.10.1 Training and Certification

A WHI CC physician, NP, or PA may perform the endometrial aspiration after completion of the WHI training and certification process. Clinical Center staff performing this procedure must be licensed appropriately to practice primary care in the state where the CC is located and comply with all state and federal regulations regarding physician supervision of their clinical practice, if appropriate. This procedure is reviewed in the training video, "Endometrial Aspiration", available from the CCC.

9.10.2 Antibiotic Prophylaxis

Antibiotic prophylaxis may be needed for select participants before the aspiration. Policy and drug selection is left to the discretion of each CC. Often, asking the participants' private physician whether prophylaxis is necessary (and the drug of choice) is the easiest and most consistent policy. In general, however, antibiotic prophylaxis before the endometrial aspiration should not be given unless:

- the participant or her physician indicates she has been given antibiotics in the past before surgical procedures and requests them for this procedure; or
- she has a prosthetic heart valve, previous history of endocarditis, rheumatic heart disease, or surgically-constructed systemic pulmonary shunt or conduit.

Antibiotic prophylaxis can be used in conjunction with artificial joints at CC discretion. *Figure E.5.8 in Appendix E shows* a model *Antibiotic and Medication Allergies Questionnaire (HRT Participants with Uteri*) assessment form for evaluating a participant's need for antibiotic prophylaxis and allergies to medications.

9.10.3 Performing the Endometrial Aspiration

Perform the endometrial aspiration in a private examination room with good lighting. This procedure should be carried out, if possible, following the pelvic exam and Pap smear. A female assistant may remain in the room if appropriate. Ask the participant to empty her bladder before the procedure. Assist the participant into the lithotomy position and be sure she is comfortable, gowned, and draped during the procedure. Always perform a bimanual examination of the uterus and adnexae just before the aspiration to verify the position and size of the uterus.

A flexible aspirator is the equipment of choice for WHI endometrial aspirations. Perform the endometrial aspiration as follows:

- Insert a speculum lubricated with warm water. Swab the cervix with betadine.

- It is recommended that you perform local paracervical and uterine anesthesia by infiltration of up to 1 cc of 1% lidocaine at each of the 4- and 8-o'clock positions of the cervical mucosa. Local anesthesia should be used particularly if the participant experiences discomfort during the procedure. If, after infiltration, she still experiences discomfort, lidocaine may also be infiltrated at the 2- and 11-o'clock positions. Alternatively, "Hurricaine gel" (benzocaine 20% gel), may be applied topically to the cervix as an anesthetic. If a participant has had problems with uterine cramping previously, she may be given a non-steroidal anti-inflammatory drug (NSAID), such as ibuprofen 400 mg by mouth, one-half hour before the endometrial aspiration, as long as she does not have any contraindication to the use of NSAIDs.
- The use of a tenaculum may be necessary to stabilize the cervix and provide counter-tension. Since many participants find the tenaculum uncomfortable, it is recommended that you use a local anesthetic (see above) if you must use the tenaculum. A small, lacrimal duct probe can be used to dilate a stenotic cervical os.
- Insert the flexible aspirator through the cervix into the uterus.
- Attempt to place the biopsy instrument at the apex of the uterus to maximize the probability of obtaining an adequate sample. Record on *Form 82 - Endometrial Aspiration* the depth (in centimeters) of the uterine cavity based on the markings on the aspirator. This measurement will be a reference to aid in instrument placement for subsequent endometrial procedures.
- Obtain endometrial tissue from all uterine surfaces by inserting, withdrawing slightly (not completely), and rotating the aspirator within the uterus. Cut the tip off the aspirator with scissors and allow the tip to fall into a formalin bottle that has been labeled with the participant's barcode label. Using the aspirator, push the specimen immediately into the same bottle.
- Forward the endometrial aspiration tissue to a local pathologist for review. Any material, no matter how scant, should be sent to the local pathologist for pathologic examination. Do not store the formalined tissue in your CC for more than two days.

Procurement of an endometrial specimen may not always be possible after entry into the uterine cavity due to atrophy.

If entry into the uterine cavity is not possible due to cervical stenosis, even after a paracervical block (and, if appropriate, an attempt by the consulting gynecologist has been made), a transvaginal uterine ultrasound can be performed. However, continue to make subsequent attempts at endometrial biopsy at the scheduled times during the follow-up exams and for vaginal bleeding (see *Section 5 - Hormone Replacement Therapy*).

Document pathology results on *Form 82 - Endometrial Aspiration*. Refer to *Volume 2, Section 5.1.2.5 – Exclusions Based on Baseline Endometrial Evaluation* for findings that would make a participant ineligible for HRT or, on follow-up, would require further work-up or treatment.

9.10.4 Performing Transvaginal Uterine Ultrasound

Schedule a transvaginal uterine ultrasound during screening or follow-up visits for a participant if an endometrial aspiration cannot be performed because of cervical stenosis. An endometrial thickness of * 5 mm will be accepted as normal (see *Section 5 - HRT*). Findings of pelvic pathology or other pathology would make the participant ineligible for HRT unless follow-up evaluation of these findings rules out malignancy. Document findings on *Form 83 - Transvaginal Uterine Ultrasound*.

9.11 Cognitive Assessment (Required)

9.11.1 Overview

Cognitive assessment is performed at baseline and follow-up visits for all HRT participants age 65 and older at baseline as outlined in *Vol. 1 - Study Protocol and Policies, Table 1-A1.1 - Frequency of Data Collection*. *Form 39 - Cognitive Assessment* is based on the NHLBI-funded Cardiovascular Health Study (CHS), an observational study of older women and men. This procedure uses the Modified Mini-Mental Status Examination (3MSE), a widely-used test of cognitive function among older people. It includes tests of orientation, registration, attention, calculation, recall, language, and visual-spatial skills. The interview-administered form does not require unusual skills or technology at the CC.

The hypothesis guiding this activity is that HRT may prevent age-related decrements in cognitive functioning (the ability to process different types of information).

The cognitive assessment procedure involves several activities:

- Training and certification.
- Preparing and assembling appropriate materials.
- Conducting the cognitive assessment interview with the participant. Note that the Benton Visual Retention Test (Benton) and Digit Symbol Substitution Tests (DSST) on the form are no longer administered.
- Scanning the completed *Form 39 - Cognitive Assessment*.

9.11.2 Training and Certification

Women's Health Initiative CC staff can perform cognitive assessment procedures after completion of the WHI training and certification process. Appropriate cognitive assessment interviewers should have good skills in probing and interpersonal communications. Clinical Centers should train and certify only two interviewers for this task, because the procedure will not be performed frequently and more than two interviewers will have difficulty staying in practice. However, this guideline is a recommendation; you may train and certify as many interviewers as needed for your CC.

The required training and certification procedures for conducting the cognitive assessment include:

- Reading the materials provided. Read through the form and form instructions. This will help you become familiar with the procedures. Try reading the interview out loud or in front of a mirror. Hearing yourself read the questions will help you to conduct the interview more smoothly. Make sure you have all necessary materials with you when you practice the interview.
- Practicing with friends, family, or other CC staff. Practice the interview twice with another person. Go through the form slowly at first, making sure that you have all the materials and that you find all the transitions from one type of question to another. The purpose of this type of practice is to familiarize yourself with the logistics of administering the form to another person. Mock participants should be asked to "stage" difficult or unusual situations for interviewers. Write questions directly onto the form for discussion with local training staff or CCC resource staff.
- Discussing problems and procedures with local training staff (or CCC resource staff). You should feel free to raise questions or concerns you might have after reading the materials and practicing the interviews. More than one discussion session interspersed throughout the training process may be beneficial.
- Conducting a formal interview session while being observed. This session will be the final step in the training and certification process. The interview should be conducted all the way through with a mock participant(s).

9.11.3 Prepare for the Interview

Before performing interviews with participants, re-familiarize yourself with the interview form, forms instructions, required materials, and procedures, particularly if you have not conducted the interview recently.

Interviewers should have the following materials available before beginning a cognitive assessment interview:

- *Form 39 - Cognitive Assessment* (with participant barcode label applied).
- One sheet of blank 8½" by 11" paper for the 3MSE with a participant barcode label applied in the top right-hand corner.
- Stopwatch and/or watch with a second hand for accurate timing on appropriate items.
- Two standard lead pencils with erasers.
- Laminated cards for 3MSE portion of the form (Card 39-1: "Close your eyes" statement and Card 39-2: overlapping pentagons), available from the CCC.
- Form instructions for reference.

9.11.4 Conducting the Cognitive Assessment Interview

Conduct the interview in a private area away from other participants, CC staff, or other distractions and at a desk or table the participant can use as a writing surface. Ask the participant if she is comfortable. Reassure her that this is a routine test of concentration and memory that will be done several times during the course of the study. It is not an intelligence test. Her responses will not be compared with other participants' responses and no individual information or participant identifiers will be reported in WHI publications. Tell the participant that some questions are more difficult than others and some questions will be asked more than once (see scripts on Form 39).

Ask each question on *Form 39 - Cognitive Assessment* in order, using the strategies and probes as described in the form instructions. Refer to *Section 2.1.4 - Interviewer Guidelines* for basic interviewing techniques such as staying neutral and probing carefully.

When the interview is completed, thank the participant and tell her she did well, without offering her specific feedback on her performance (the WHILMA database will score her responses). You might say, "*Thank you for doing this interview. You did just fine.*" Scan the completed form (note that the Benton and DSST sections of *Form 39 - Cognitive Assessment* will be blank).

Section 9
Clinical Measurements

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SECTION 10

DIETARY ASSESSMENT

INTRODUCTION

Assessment of nutrient intake in free-living populations is a difficult problem in dietary intervention research. There are no "gold standard" or criterion measures, and assessment methods differ in reliability, accuracy, costs, participant burden, and susceptibility to bias. Three instruments are used to monitor food and nutrient intake in WHI: (1) the Food Frequency Questionnaire, (2) the food record, and (3) the dietary recall.

Form 60 - Food Frequency Questionnaire (FFQ) assesses group and individual-level intakes of selected nutrients, in particular the proportion of total energy from different macronutrients. The FFQ is self-administered and inexpensive to process. However, the fixed list of foods may not be appropriate for all participants, some women find it difficult to estimate frequency of intake and portion sizes, and this instrument provides no information on eating patterns or all nutrients.

Form 62 - Four-Day Food Record (4DFR) is an open-ended assessment instrument that provides detailed data on food consumption and can estimate intake of total energy, nutrients, and food components such as fatty acids and carotenoids. However, food records can be subject to bias because the participant may change what she eats during the period she is keeping records. This potential bias is a particular concern in dietary intervention studies. In addition, this assessment instrument has high participant burden and is expensive to administer and analyze.

24 Hour Recall (24HR) - Like a food record, the telephone-administered 24-hour dietary recall provides detailed information about a participant's food and nutrient intake. However, because participant's cannot change what they ate retrospectively, no alteration in usual diet should occur. This assessment technique has lower respondent burden than a food record, but does rely on participants' memory. Because the recalls are administered and analyzed centrally by the CCC, the technique is more standardized and somewhat less expensive than a food record.

From a scientific perspective, the major disadvantage of records and recalls is that they only measure short-term food intake, which may not reflect usual diet. Multiple days of records or recalls can improve the estimate of usual diet, but dramatically increase respondent burden and costs. Therefore, in this study, we use all three assessment methods (FFQs, records, recalls) to minimize cost and participant burden, while providing appropriate and state-of -the-art data to aid in study evaluation.

The FFQ is used to assess dietary intake of all participants at baseline, to screen participants for eligibility into the DM, and to assess dietary intake of participants at follow-up visits. The 4DFR is used at baseline to assess the participant's ability to participate in the DM Intervention. The food record is also used to assess diet in a DM cohort subsample at baseline and one-year follow-up. To minimize clinic and participant burden, the cohort follow-up at years 3, 6, and 9 consists of two centrally administered 24-hour dietary recalls. Finally, a dietary recall is administered to a one percent random sample of participants each year to assess control and intervention group differences in the DM. A small proportion of these participants receive two recalls to allow us to assess intra- vs. inter-variability in intake, use that information to adjust our nutrient variance estimates, and thereby estimate the distribution of nutrient intakes in the sample.

Together, these measures support hypotheses related to the effects of dietary intervention on nutrient intake, maintenance of intervention-control group differences, and associations of nutrient intake with biochemical parameters, morbidity and mortality.

The Clinical Coordinating Center (CCC) uses the University of Minnesota's Nutrition Data System (NDS) for entry and analysis of dietary assessment data collected for the Women's Health Initiative (WHI). The NDS consists of data entry software, analysis software, and a comprehensive food and nutrient database, which is updated annually by the University of Minnesota Nutrition Coordinating Center (UM-NCC). The data entry software provides standardized prompts for entering dietary records, thus standardizing data entry procedures

and increasing the comparability of the data across Clinical Centers (CCs). The NDS is used for data entry of all dietary data collected by the 4DFR and the 24HR; the food and nutrient database is used in the analysis of FFQs, allowing for comparison of various methods of dietary assessment for WHI.

10.1 The Four-Day Food Record (4DFR) (Required)

The *4DFR* is a detailed documentation of the food that the participant eats over four days. The main objective of the *4DFR* is to obtain a complete list of a participant's dietary intake during the selected time period. The *4DFR* is kept by the participant, ideally as she consumes her meals and snacks, for a period of four alternate days (e.g., Monday, Wednesday, Friday, Sunday). This method provides the most detailed, individual-level data on nutrient intake of all of the dietary assessment tools used in the DM. It provides the most accurate individual assessment of total energy, macronutrients, micronutrients and specific food components such as types of fatty acids. Food records also provide the best information on culturally-specific foods and food preparation methods. They are, however, subject to potential bias because study participants may change what they eat during the record-keeping period and four days of records may not reflect "usual diet."

A more accurate picture of true dietary intake would be obtained from a longer period of record keeping (e.g., seven or even 14 days). However, this is not practical due to excessive burden on the participants and extensive costs to the DM in terms of documenting and coding the additional days. Four days are a commonly-accepted representation of an individual's usual macronutrient intake and are frequently used in research settings. For key nutrients in WHI, such as dietary fat, four days provide an adequate estimate of intake. We selected alternate day record-keeping rather than four consecutive days for several reasons. Alternate days yield better estimates of usual intake, due to the correlation (often negative) between sequential days. Also, we found in previous studies that participants find it less burdensome to keep records every other day. Lastly, using alternate days allows a participant to begin her record on any assigned day and still include a weekend day. This adds considerable flexibility to CC schedules and follow-up CC visits, and gives the participant a more personal choice on when to begin her record.

Food records are kept by all potential DM participants between the Screening Visit 2 (SV2) and Screening Visit 3 (SV3), and by a subsample of the DM participants at the annual CC visit in year 1. At baseline (before randomization) the records serve as part of the determination of a woman's willingness and ability to participate in the detailed tasks of the DM. At baseline and during follow-up DM visits these records also provide estimates of individual nutrient intake and dietary change for a subsample of DM participants. The *4DFR* subsample is identified at the time of randomization. The *4DFRs* from this subsample are documented, peer reviewed and analyzed.

The *4DFR* booklet consists of the following sections:

- The front page for the participant's name, assigned dates for keeping the record, name and telephone number of the CC contact person, and the next appointment date and time.
- Two pages of instructions on keeping accurate *4DFRs*.
- A page requesting information on the vitamin and mineral supplements taken during the record-keeping period.
- A page of general questions on types of fats and oils used throughout the *4DFR*.
- A sample day's record.
- A number of lined pages on which to list and describe the foods and beverages consumed during the record-keeping period and columns to designate the meal, place prepared (home, restaurant or other) and the amount eaten.
- A few pages for detailed listing of recipes prepared during the assigned days.
- A shaded box on the back page for specific data items ("Office Use Only").

Adjacent to each page on which the participant records her food intake is a lined page for CC Dietary Assessment staff to document and describe in detail the foods and beverages consumed, and two columns to document fat added to foods in preparation and at the table (see *Section 10.1.4 - Baseline Food Record Documentation*). This documentation is critical for accurate representation of what the participant actually ate during the specified time period. Participants often do not provide adequate detail on food preparation or the amount of food they eat. In addition, it is common to forget to include condiments or beverages consumed

with meals, and fats added in preparation or at the table. The CC Dietary Assessment staff is responsible for obtaining this information in detail at the time the record is documented with the participant.

10.1.1 Activities at SV2

All potential DM participants keep a *4DFR* between SV2 and SV3. Dietary Assessment staff certified for the *4DFR* show the WHI video "Keeping Track of What You Eat" to all potential DM participants. The video instruction should take 20-25 minutes and covers:

- General instructions for keeping food records.
- How to describe foods and beverages consumed, including ingredients used in preparation and preparation methods.
- How to measure and/or estimate quantities consumed.
- How to describe homemade recipes and foods prepared by others.
- The importance of not changing one's eating habits and recording everything one eats during the record keeping period.

After the participant watches the video, Dietary Assessment staff certified for the *4DFR*:

- Answer questions.
- Distribute the *4DFR* and *Form 69 - Keeping Track of What You Eat* and show participants the sample records printed in these materials.
- Provide measuring cups and spoons to women who do not have these materials at home.
- Ask participants to practice recording a meal and review it for adequacy of completion.
- Assign four alternating days and dates for the participant to keep her *4DFR* and write this information on the front of the *4DFR*.

The participant must complete the *4DFR* before SV3. CC staff apply a computer-generated label containing the woman's ID number and visit number to the back of each *4DFR* before distribution.

10.1.2 Activities at SV3

Before randomization, a certified Lead Nutritionist, Dietary Assessment staff or Group Nutritionist must use the *DM Eligibility Checklist* to assess a woman's ability and willingness to complete the DM Intervention activities. This review process takes approximately 20 minutes. For detailed instructions on this review process and a copy of the *DM Eligibility Checklist*, see *Section 6.2 - SV3 Assessment of DM Eligibility*.

Following randomization, Dietary Assessment staff, certified for the *4DFR*, document individual *4DFR*s for women identified in the *4DFR* subsample of the DM. Post SV3, a second Dietary Assessment staff member, certified for the *4DFR*, reviews the *4DFR* as described in *Section 10.1.8.1 - CC Documentation and Peer Review Procedures for Documented 4DFRs*.

10.1.3 Follow-Up Visit Record Completion

The participants in the *4DFR* subsample are asked to keep a *4DFR* at the annual CC visit in year 1. Participants in this subsample are selected at the time of randomization. Clinical Center staff can print a participant visit plan from WHILMA before the annual visit. The visit plan identifies whether a woman is to keep a *4DFR* before the annual visit. Two weeks before the annual visit, CC staff:

- Contact the participant to inform her that she will need to complete a *4DFR*.
- Assign the days on which the *4DFR* is to be kept and write the days and dates on the front of the *4DFR*.

- Affix the participant ID label with barcode to the back of the *4DFR*.
- Mail the *4DFR* and instruction pamphlet *Form 69 - Keeping Track of What You Eat* to the participant along with the other forms mailed two weeks before the annual visit.

The woman brings the completed *4DFR* with her to the annual visit and meets with Dietary Assessment staff certified for the *4DFR* who documents the *4DFR*.

10.1.4 Baseline Food Record Documentation

Dietary Assessment staff certified for the *4DFR* document the completed *4DFR* with each participant identified in the *4DFR* subsample. Ideally, staff are completely blinded to the randomization status of the participant. If this is not possible, ensure that the documentor is blinded until after the *4DFR* is documented. The randomization status should not be revealed to the participant until documentation of the *4DFR* is complete. It is also important to document the *4DFR* as soon as possible after the last day of recording to maximize the woman's memory of what she ate during the record-keeping period. Documentation of the *4DFR* should take 30-45 minutes to complete.

Complete descriptions of foods, preparation methods, ingredients, and portion size are critical in the accurate assessment of dietary intake. Dietary Assessment staff should use the following guidelines to document *4DFRs*:

- Use the *WHI 4DFR Documentation Checklist* to document the *4DFR* with the participant. See *Figure 10. 1 - WHI 4DFR Documentation Checklist*.
- Obtain brand names for food products indicated whenever possible. This information is particularly important for fats and oils, fat modified products, and commercial frozen entrees.
- Probe for spreads, sauces, and fillings that may be sources of additional fat.
- Carefully check portion sizes and dimensions provided by the participant.
- Use the Fat Added Columns to document sources of fat consumed by the participant (see *Figure 10.2 - Guidelines for Documenting the Fat Added Columns of the 4DFR*).

A second Dietary Assessment staff certified for the *4DFR* reviews each *4DFR* before sending the records to the CCC for processing (see *Section 10.1.8.1 - CC Documentation and Peer Review Procedures for Documented 4DFRs*).

10.1.5 Follow-Up Visit Food Record Documentation

Dietary Assessment staff certified for the *4DFR* document the completed *4DFR* with the participant at the CC annual visit. Ideally, at the follow-up visit, the documentor is blinded to the DM randomization status of the woman; at a minimum, the documentor must not be the Group Nutritionist for the participants whose *4DFRs* she documents. A second Dietary Assessment staff certified for the *4DFR* peer reviews each *4DFR* before sending the records to the CCC for processing.

The 4DFR data collected at AV1 is a critical evaluation tool. The four-day food records provide information on control minus intervention differences at the one-year visit and are an important check on the reliability of the data from the FFQ. To be accurate, the record must be reflective of the participant's dietary intake at the one year timepoint. This is important for two reasons: (1) because of the potential for drift to a higher fat diet post-intervention, and (2) to capture data on temporal changes in the diet of control participants.

Every effort should be make to collect the 4DFR at the annual visit. If an annual 4DFR is NOT completed within six months after the annual visit (e.g., due to participant/family illness, lost 4DFR, unable to contact participant, scheduling difficulties, etc.) staff can discontinue efforts to obtain the 4DFR. The Lead DA Nutritionist should email the CCC Dietary Assessment Research Nutritionist the participant ID# and the reason the 4DFR will not be sent to the CCC. These 4DFRs will be recorded as "missing data".

10.1.6 Common Problems and Solutions

10.1.6.1 A Participant Does Not Complete Her Baseline 4DFR

If the baseline *4DFR* is partially complete, make every attempt to complete the record with the woman while she is in the CC. A *4DFR* with 3-days is acceptable. However, if fewer than three days are recorded, randomization should be delayed until the participant completes an acceptable *4DFR*. Ask the woman to complete the record in the upcoming week and re-schedule the randomization visit. If the woman does not return the *4DFR*, she is not eligible for DM. Complete the Staff Impression for DM question on *Form 6 - Final Eligibility Assessment*. Mark the "ineligible" box and enter staff ID code. Record the reason as "Did not return *4DFR*".

10.1.6.2 A Participant Fails to Return Her Follow-Up 4DFR

Dietary Assessment staff should make every effort to obtain a completed *4DFR* from participants in the *4DFR* subsample. If a participant completes her follow-up *4DFR*, but does not bring it with her to the CC annual visit, give her a stamped envelope for return. If a participant has not completed her follow-up *4DFR*, give her another *4DFR*, assign new days and dates for completion, and provide a stamped envelope for return. Ask the participant to make a copy of the completed 4DFR so that she will have it to refer to when the documentor calls to clarify the information she has recorded. Dietary Assessment staff certified for the *4DFR* document the *4DFR* by telephone as soon as the record is received. If the *4DFR* is not received within two weeks after her CC visit, call the participant and ask her to mail the *4DFR* as soon as possible. If the *4DFR* is not received within three weeks after her CC visit, make a second reminder telephone call.

10.1.6.3 A Baseline 4DFR is Unacceptable

If a *4DFR* is determined to be unacceptable (see *Section 6.2 - SV3 Assessment of DM Eligibility*), thank the woman for her interest and explain that she is ineligible for the study.

10.1.6.4 A Participant is Sick During the Record Keeping Period

If a woman is sick during the entire week of her *4DFR*, ask her to call the CC and reschedule her *4DFR* days. However, if she is sick for only one day she should keep the *4DFR*, and make note of her illness on the day she is sick.

10.1.6.5 A Participant Does Not Record Alternate Days of Intake

The importance of recording alternate days of intake should be stressed to participants at SV2. However, a *4DFR* kept on consecutive days is acceptable.

10.1.7 4DFR Processing

10.1.7.1 CC Procedures for Processing Documented 4DFRs

Clinical Center staff:

- Peer review all documented *4DFRs* for the subsample of DM participants (see *Section 10.1.8.1 - CC Documentation and Peer Review Procedures for Documented 4DFRs*).
- Key-enter the shaded section on the last page of each *4DFR* into WHILMA (see *Vol. 5 - Data System, Appendix B.3. - Step-By-Step Task Instructions*).
- Photocopy all *4DFRs* of participants who are in the *4DFR* subsample and file the copies at the CC. This is essential for two reasons: 1) When the CCC requests clarification or additional information, the CC has a copy of the record to refer to, and 2) a copy is available in case an original is lost in the mail or elsewhere.

- Complete the *4DFR* packing slip.
- Send the original *4DFRs* for the subsample of DM participants to the CCC weekly via Federal Express.
- File the copies of documented *4DFR*s for the *4DFR* subsample and all original non-documented *4DFR*s at the CC.

10.1.7.2 CCC Procedures for Processing Documented 4DFRs

- Log each *4DFR* into the database upon receipt using the procedures described below.
- Analyze all *4DFR*s collected from the subsample of women in the DM using the NDS.
- Send *Form 68 - Food Record Inquiry* to the CC Lead Nutritionist when food items or quantities in the *4DFR* need clarification.
- Send a 5% sample of analyzed *4DFRs* to the UM-NCC annually. UM-NCC re-analyzes these food records and provides feedback regarding discrepancies in data entry of *4DFRs* to the CCC as a quality assurance procedure.
- Archive all original documented *4DFRs* for the *4DFR* subsample at the CCC.

10.1.7.3 CCC Review Procedures for Documented 4DFRs Received from the CCs

The CCC Data Control Technician reviews each *4DFR* received from the CCs using the *4DFR Screening Checklist* and:

- Forwards acceptable *4DFRs* to the Nutrition Assessment Shared Resource Unit (NASR) for data entry and analysis of nutrient intake. The NASR provides trained and certified staff to process *4DFR* data using standardized data-entry procedures.
- Notifies the CC Lead Dietary Assessment Nutritionist by email which *4DFRs* are unacceptable and the specific error to be corrected.

A *4DFR* is unacceptable by the CCC for any one of the following reasons:

- Illegible *4DFR*. See *Section 10.1.2 - Activities at SV3.*
- Less than three days of records. See *Section 10.1.2 - Activities at SV3.*
- Entire section for Vitamin and Mineral Supplements (page 4) incomplete and/or supplements not recorded on the days taken in the daily record.
- Entire section for General Questions (page 5) incomplete.
- Shaded section on the back of *4DFR* booklet (page 40) incomplete and/or data items incorrectly key-entered (see *Vol. 5 - Data System, Appendix B.3. - Step-by-Step Task Instructions*).

10.1.7.4 Lead Nutritionist Procedures for Unacceptable Documented 4DFRs

The CC Lead Nutritionist:

- Reviews the items identified by the CCC Data Control Technician with the original documentor and the peer reviewer.
- Instructs the documentor to complete the documentation specified and contact the participant if necessary.
- Emails the information requested to the CCC Data Control Technician within five working days of receipt.

10.1.8 Quality Assurance of 4DFRs (Required)

Quality assurance is based on procedures developed and tested for the Women's Health Trial Feasibility Study in Minority Populations. These procedures were developed and are maintained as a cooperative activity among the CCs, the CCC and the UM-NCC. To assure high quality food intake data, the CCC monitors all CC *4DFR* collection and documentation activities using the procedures described in the following sections.

10.1.8.1 CC Documentation and Peer Review Procedures for Documented 4DFRs

Within each CC, quality assurance will be based on peer review. After a Dietary Assessment staff member documents a *4DFR* with the participant, a different Dietary Assessment staff member reviews the *4DFR* within three working days of the date documented. In this way, most problems can be corrected before the *4DFR* is analyzed and archived by the CCC. It is important that all CC staff involved in the collection of *4DFRs* develop and maintain a high level of proficiency in accurate and complete documentation of *4DFRs*.

- Dietary Assessment staff must use the *WHI 4DFR Documentation Checklist* (see *Figure 10.1 - WHI 4DFR Documentation Checklist*) to document the *4DFR* with the participant and to conduct the peer review.
- The *4DFR* Screening Checklist (see *Figure 10.3 - 4DFR Screening Checklist*) must be used by staff who conduct the peer review.

10.1.8.2 4DFR Documentation Performance Standards

Acceptable performance for documentation and peer review of *4DFR*s is defined as:

- Fewer than four documentation errors *(Form 68 - Food Record Inquiry)* per booklet for 75% of *4DFRs* documented.
- Fewer than six unacceptable *4DFRs* per year (see *Section 10.1.7.3 - CCC Review Procedures for Documented 4DFRs Received from the CCs*).

The *Dietary Assessment Quality Assurance Reports* monitor these standards. Additional training is required for documentors who are unable to meet these performance standards.

10.1.8.3 Dietary Assessment Quality Assurance Reports

The CCC prepares quarterly Quality Assurance Reports for each CC. Data for the reports are compiled from *Form 68 - Food Record Inquiry* and the *4DFR Screening Checklist*. These reports provide feedback to the CC Lead Nutritionist on the accuracy of *4DFR* documentation and monitor the performance of Dietary Assessment staff certified for the 4DFR. A description of each report follows:

- **Clinic Performance for Books Archived (*WHIP 0935):*** Details the occurrence of each documentation error type within the 4DFR books archived (documented) for each WHI Clinical Center. Data for this QA report is compiled from *Form 68 - Food Record Inquiry*.

- **Documentor Performance for Books Archived (*WHIP 0940*):** Details the total number of *4DFR* books archived (documented) and the number of errors found within those books for each CC Dietary Assessment staff. Data for this QA report is compiled from *Form 68 - Food Record Inquiry*.

- **4DFR Screening Checklist Error by Clinic *(WHIP 0949)*:** Details the occurrence of each screening error type within the *4DFR* books archived (documented) for each WHI Clinical Center. Data for this QA report is compiled from *Figure 10.3 - 4DFR Screening Checklist*.

- **4DFR Screening Checklist Error by Employee (*WHIP 0950*):** Details the occurrence of each screening error type within the 4DFR books archived (documented) for each CC Dietary Assessment staff. Data for this QA report is compiled from *Figure 10.3 - 4DFR Screening Checklist.*

10.1.8.4 Quality Assurance of 4DFR Data Entry (Required)

The UM-NCC provides quality assurance services for the coding and data entry activities at the CCC. The UM-NCC will process a 5% sample of all analyzed *4DFRs* using a comprehensive software system to compare double-entered NDS records. The CCC reviews reports from this system and conducts supplemental training as needed for NASR staff. The CCC Dietary Assessment Supervisor also meets regularly with the NASR Manager and Coding Nutritionists to review coding questions and documentation errors.

10.2 The FFQ (Required)

The *FFQ* is labeled Food Questionnaire for ease of understanding by the participant. The *FFQ* is used to assess usual dietary habits. It is a self-administered assessment of the participant's usual food intake over the previous three months. The *FFQ's* main purpose is to assess group-level and individual-level intakes of selected nutrients, in particular the percent of total kilocalories from macronutrients, beta-carotene, vitamins C, E, and A, dietary fiber, calcium, and iron.

The *FFQ* is used as a screening tool for the DM component of the trial at SV1. Women are ineligible for DM if their *FFQ* nutrient analysis report is (1) less than 32% calories from fat, or (2) less than 600 kcalories, or (3) more than 5,000 kcalories. (See *Section 6.1 - DM Eligibility Issues.*) The screening *FFQ* becomes the baseline *FFQ* for women entering any WHI component. During the study the *FFQ* will be administered according to the schedule in *Figure 2.1 - Frequency of CC Tasks*.

The *FFQ* includes a data section, participant instructions, and three sections on food. Each section has different questions:

- The data section is on the front page. Clinical Center data staff complete the shaded area (see *Vol. 3 - Forms, Instructions for Form 60*).

- Page 2 contains written instructions for the participant and an example.

- The first section of the *FFQ* (pages 2-4) consists of 19 questions on types of foods and preparation methods which permit the analysis software to interpret the use of specific food items.

- The second section of the *FFQ* (pages 5-11) includes individual food items arranged in food groups and, for each item, the participant indicates the usual portion size and frequency of consumption. Frequency choices range from "never or less than once per month" to "2+ times per day" for food items, and "6+ times per day" for beverages. The portion size allows the participant to choose between "small, medium and large." A medium serving size is given as an example on the *FFQ*; a small serving is equal to one-half of the medium serving or less, and a large serving is equal to one-and-one-half times the medium serving or more.

- The third section consists of four summary questions which ask about the usual consumption of fruits, vegetables and fats used in cooking. When given a list of foods, people often report eating more foods in a given category than they actually consume. Answers to the summary questions permit the analysis program to adjust responses to individual item frequencies so that the sum of all items in a food group are the same as the reported usual frequency of consumption for these foods.

It is not possible for the *FFQ* to incorporate all the foods that people eat. The food items on the *FFQ* were chosen using the following criteria: (1) data-based identification of major contributors of macro- and micro-nutrients in the US diet (Block etal. Am. J. Epidemiol 1985:122:13-20); (2) adequate items to reflect regional and ethnic eating patterns; (3) enough low-fat and fat-free modified foods to capture intervention results, and (4) incorporation of suggestions made by the Vanguard Clinical Centers (VCC). The *FFQ* is not intended to ascertain specifically what a person eats, but rather to get an overview of a woman's usual pattern of food intake (i.e., her usual frequency of consuming the listed foods and beverages).

Form 61 - How to Fill Out the Food Questionnaire provides additional instructions and nine pictures depicting small, medium, and large servings of three food items to help the participant estimate usual portion sizes to complete the serving size column of the *FFQ*. This is the only instruction sheet to be used for the *FFQ*.

10.2.1 Distributing and Completing the FFQ

The mailing, processing and storage of the *FFQ* is the responsibility of the CC. The baseline (screening) *FFQ* can be mailed to all potential participants and returned by the participant at or before the SV1 to determine

DM eligibility. Clinical Centers may also use the Screening Visit 0 (SV0) for distribution and/or completion of the *FFQ*. See *Section 3.7 - Visit (SV0)*. Follow up *FFQ*s are mailed to participants identified in the *FFQ* subsample before all follow-up CC visits, completed and returned to the CC at the scheduled annual visit.

The *FFQ* is a mark-sense form and must be completed using a #2 pencil. The form should not be folded or it will not scan properly.

10.2.1.1 Baseline (Screening) FFQ

All women who are interested in the trial complete an *FFQ* no later than SV1. Clinical Centers that mail the *FFQ* should use the procedures listed in *Section 3.6 - Mailing Initial Baseline Forms.*

10.2.2 Processing the FFQ

The CCs process the completed *FFQs* during the CC visit. This allows the reviewer to return the *FFQ* to the participant for completion or clarification and immediately identifies participants who are eligible (or ineligible) for the DM component. If screening *FFQs* are returned by mail before SV1, Dietary Assessment staff may need to call the participant to clarify any issues before determining eligibility.

Clinical Center staff certified for the *FFQ* review the completed *FFQs*. See General Instructions (#4) for the *FFQ*. The data staff scans the *FFQ* using the OpScan5 (see *Vol. 5 - Data System, Section 7.2 - Scanning*).

10.2.3 Reviewing and Editing the FFQ

Editing the *FFQ* involves the following:

- Cursory Review
- Pre-Scan Edit
- Computer Scanning of the *FFQ*
- Post-Scan Edit

10.2.3.1 Cursory Review

A cursory review is done quickly to catch obvious errors, such as large amounts of missing data or handwritten notes. This review should take no more than 30 seconds unless there are stray marks, handwritten items or numerous ovals that need to be darkened. Complete the Cursory Review using the procedures specified in General Instructions (#4.1. - 4.4.) for the *FFQ*. If there are many missing items (see *Section 10.2.5 - FFQ Error Report*), the reviewer should declare the *FFQ* unacceptable before it is burst and scanned. Return the unacceptable *FFQ* to the participant for completion.

10.2.3.2 Pre-Scan Edit

The pre-scan edit is conducted by a staff person certified for *FFQ* review (see *Form 465 - Food Frequency Questionnaire Certification*). A thorough review includes checking the form for inconsistencies, multiple marks and missing items, in addition to the items completed during the cursory review. The *FFQ* reviewer does not need to check each individual food item because the computer scanner can find double marks and count the number of missing items more accurately and efficiently. This review should take about two minutes, but it may take longer if many items need clarification by the participant. Complete the pre-scan edit using the procedures specified in the General Instructions (#4.5. - 4.7.) for the *FFQ*.

10.2.3.3 Guidelines for Interviewing Participants

Clinical Center staff certified for the *FFQ* may need to clarify information with the participant following the pre-scan and post-scan edits (see *Section 2.11.4.1 - Interview Techniques*). Use the guidelines below to facilitate the interview and obtain the information needed in an unbiased manner:

- Use non-leading questions (i.e., those that do not suggest an answer but guide the participant to report actual intake). See *Section 10.2.3.4 - Non-Leading Questions.*
- Ask one question at a time and concentrate on listening carefully to the answers rather than thinking ahead to the next question.
- Allow adequate time for the participant to think about her responses.
- Be neutral in your responses and avoid communicating verbal or nonverbal approval/disapproval of the participant or her dietary intake.
- Rephrase questions when the participant hesitates or does not seem to understand the question.
- Do not offer advice or dietary counseling.

10.2.3.4 Non-Leading Questions

Use the following examples as a guide to clarify responses with the participant:

Missing Food Items

- "There are several blank items on this page of the Food Questionnaire. It is important that each food item have a response. Please look at the foods you didn't mark. If you did not eat the food in the last three (3) months, fill in the oval under the column called 'never or less than once per month.' If you ate the food in the last three (3) months, please mark 'how often' you ate the food and the 'amount' you ate. Thank you."

Same Frequency Marked for a Substantial Number of Foods

- "Would you please look at the foods on this page of the Food Questionnaire again. Think about 'how often' you ate each food during the last three (3) months. Be sure your answer shows how often you ate each food during this time. Thank you."

Same Portion Marked for a Substantial Number of Foods (e.g., all "small" portions)

- "Would you please look at this page of the Food Questionnaire again. Please look at the medium serving size listed for each food. Think about how it compares to the amount you ate. If you ate this amount, your serving size is 'medium.' If you ate **half** this amount (or less) your serving size is 'small." If you ate more than **(1 and 1/2 times)** this amount, your serving size is 'large.' Please review the amounts you marked again. Thank you."

Multiple Marks

- "This question can have only one response. You have marked more than one response (oval). Please read this question again and choose one response. Thank you."

10.2.4 Computer Scanning of the FFQ

Scan the completed *FFQs* according to procedures specified in *Vol. 5 - Data System, Section 7.2.2 - Some Tips for Successful Scanning* and *Section 7.2.3 - Scanning a Mark-Sense Form*. If analysis of the *FFQ* is successful, a report is generated indicating whether the participant is eligible (or ineligible) for DM. If the analysis of the *FFQ* fails, an *FFQ Error Report* is automatically sent to the printer. Clinical Center staff give

the *FFQ Error Report* and the *FFQ* to CC staff certified for *FFQ* review. This person conducts the post-scan edit using the procedures specified in *Section 10.2.5.1 - Post-Scan Edit*.

10.2.5 FFQ Error Report

The *FFQ Error Report* indicates that the form was scanned, but not analyzed, and therefore results such as eligibility cannot be determined (see *Figure 10.4 - Sample of FFQ Error Report*). Errors for individual *FFQs* are listed only if they require judgments by the CC staff or if they are sufficient to make an *FFQ* unacceptable. Thus if only a few food items are missing in a section, they will not be listed on the *FFQ Error Report*. Error conditions identified by the computer scanner and listed on the *FFQ Error Reports* are outlined below:

- Any adjustment question or sub-question (pages 2-4 of the *FFQ*) not completed.
- Any summary question (page 12 of the *FFQ*) not completed.
- Multiple marks for any food item (pages 5-11 of the *FFQ*, Frequency of Consumption Column only).
- Multiple marks for any adjustment question or any adjustment sub question requiring a single response.
- Less than 90% of the frequency fields are completed on the entire *FFQ* or more than half of the food items in any section have a missing frequency.
- Less than 90% of the food items are completed on the entire *FFQ*.

All errors identified on the *FFQ Error Report* must be corrected before the *FFQ* is rescanned. Some errors may be corrected according to the procedures listed in the following section. For other errors it may be necessary to contact the participant for clarification.

10.2.5.1 Post-Scan Edit

Clinical Center staff certified for *FFQ* review correct each error on the *FFQ Error Report* using the procedures specified below. The corrected *FFQ* is then rescanned. *Note:* The *FFQ* should be rescanned only in response to an *FFQ Error Report*. Clinical Center staff should not query participants declared ineligible.

The most common errors identified on the *FFQ Error Report* are for missing data and multiple marks.

- **Missing Data Errors**

  The *FFQ Error Report* notes excessive blanks in any section of the *FFQ* (including the adjustment questions on pages 2-4 and the summary questions on page 12). Clarify missing data errors (e.g., missing food items, missing frequencies, missing portion sizes, and missing responses to adjustment and summary questions) with the participant using the guidelines provided in *Section 10.2.3.4 - Non-Leading Questions*.

- **Multiple Mark Errors**

  Multiple marks refer to situations where the participant marks (1) two adjacent items on a single line (e.g., two frequencies are marked for one food), or (2) more than one response for any adjustment question (or sub-question) requiring a single response. Clarify multiple mark errors with the participant if she is present in the CC using the guidelines provided in *Section 10.2.3.4 - Non-Leading Questions*. Otherwise, correct the multiple marks using the guidelines provided in the General Instructions (4.6.) for the *FFQ*.

  Note: These errors may also indicate the *FFQ* was completed using pen rather than pencil. If that is the case, pull the original *FFQ* and use a #2 pencil to mark over those items completed in pen. When rescanned, the scanner should pick up the pencil marks.

10.2.6 FFQ Analysis Results

All *FFQs* that pass the error checks are analyzed to provide nutrient intake data. This information is not given to the participant. Clinical Center staff may tell women who are ineligible only that the amount of fat reported is too low for the study, or that the kcalories reported are "out of range" for the study.

10.2.7 FFQ Storage

Store the scanned *FFQ* in the participant's file or in an easily retrievable manner.

10.2.7.1 Follow-Up FFQs

A subsample of participants in the DM complete the *FFQ* at the annual CC visit (see *Figure 2.1. - Frequency of CC Tasks*). OS participants complete the *FFQ* at their three year visit. Clinical Centers mail the *FFQ* and *Form 61 - How to Complete the Food Questionnaire* to women identified in the *FFQ* subsample along with other questionnaires for completion before the CC visit (see *Section 16.3.3.2 - Two Weeks Before the Annual Visit*). Women complete the *FFQ* at home and bring it with them to the annual visit. If a participant has not completed her *FFQ*, ask her to do so at the CC visit. Process the completed *FFQ* according to the procedures in *Section 10.2.3 - Reviewing and Editing the FFQ*.

10.3 The 24HR (Required)

The 24-hour recall is an attempt define and quantify food intake during the day just before the interview. Interviews begin at breakfast of the preceding whole day and work forward. Telephone interviews are conducted by trained interviewers at the Clinical Coordinating Center using a standardized data entry software (NDS), probing techniques, and portion size tools. A random ten percent sample of all interviews are monitored by a research nutritionist or interview specialist to ensure the quality of interviewing techniques and data collection. Some advantages of the dietary recall are that the technique is open-ended; participants need not be literate; and they cannot change what they ate retrospectively, therefore no alteration in usual diet should occur.

Recalls are administered annually to a random one percent (1%) sample of DM participants (with replacement) beginning 6 months post-randomization. The sample is stratified by treatment (Intervention and Control); 43% complete two recalls, the remainder complete only one. The cohort subsample of DM participants complete two dietary recalls at years 3, 6, and 9. In the 24 HR cohort, the recalls will be separated by no more than 3 weeks and reflect weekdays and weekends. The size of the 24-hour recall sample allows study-wide estimation of the intervention effect, and the repeated recalls allow estimation of the intra-individual variability and thus statistical adjustment of the variance.

CC staff should inform women in the DM that there is a small probability that they will be called to provide this information. Clinical Centers are responsible for updating WHILMA to reflect changes in participant address and phone number.

10.3.1 CC Procedures for 24HR Cohort

- Discuss the potential of completing the 24 hour recall with DM-interested women during administration of the DM Consent. (See Vol. 1 for Revised DM Consent Form).

- Give participants in the 24HR Cohort the one page information update to read at their next visit. (See the new Model Summary of Changes for Participants in the 4DFR Subsample Appendix E.5.13).

- Develop a tracking system to ensure that participants in the 24HR Cohort receive this information.

- Print *WHIP0963 – 4DFR Cohort Participants Due for Annual Visit 3, 6, or 9* monthly and verify phone number, address, and preferred language for each participant listed. Key enter new information into WHILMA before the last working day of each month. Database updates ensure current participant information for the 24 HR telephone interview.

10.3.2 CCC Procedures for 24HR

- Mail each participant a personal letter advising them that staff from the WHI Coordinating Center in Seattle will call to conduct one or two short interviews in the next few weeks.

- Mail each participant a portion size booklet. This booklet contains pictures of commonly consumed foods in several different serving sizes, a graphic of an eight ounce glass, a ruler, and a meat thickness indicator. Participants use this booklet to help estimate portion sizes during the telephone interviews.

- Send a thank you letter to each participant after the 24HR recalls are completed.

Figure 10.1

WHI 4DFR Documentation Checklist

Food Group:	Did You Specify:	Did You Probe for Additions and Amounts of:	Preferred Serving Size Measure:
Beverages			
Coffee, Tea	Brewed, instant, decaf, herbal, cereal type (i.e., Postum)	Sweetener, whitener, cream (type)	vol
Cocoa	Type (i.e., regular, sugar-free or low-cal) Made with milk (% fat) or water	Marshmallows Whipped topping (dairy or non-dairy)	vol
Beer	Regular, light or low alcohol		vol; can
Liquor, Mixed Drinks, Liqueur	Name of mixed drink/liqueur Amount of liquor and amount of mixer With or without ice If margarita, blended or strained	Mix (juice, other non-alcoholic beverage) Cherry, olive, etc.	vol
Wine	Dinner or dessert, red or white		vol
Carbonated Beverages	Cola or non-cola, caffeine-free, diet With or without ice		vol
Cafe Mochas	Specify with or without whipped cream Specify if made with chocolate syrup or cocoa powder		vol
Dairy/Non-Dairy Products			
Milk, Cream, Coffee Creamer, Toppings	% fat, dairy or non-dairy, If non-dairy: powder, liquid or aerosol If evaporated: diluted or undiluted	Sweetener, cocoa mixes, etc.	vol
Cheese	Natural or processed Kind (i.e., Cheddar, Swiss, etc.) If low-fat, brand or % fat If mozzarella, whole, part skim, or skim milk If parmesan, dry or fresh		wt; cube; wedge; vol if grated
Yogurt	% fat, plain or flavored Frozen or refrigerated	Fruit, nuts, etc.	vol; wt of container
Ice Cream, Ice Milk, Frozen Treats	Flavor % fat, hard or soft If cone, specify type (i.e., sugar, wafer, waffle, etc.)	Topping or Coating	vol * if standard size bar, specify number
Milk Shakes, Malts	Homemade or restaurant Flavor Ice cream or ice milk Specify if non-fat		vol * if restaurant, specify sm, med, or lg
Egg, Egg substitute	Method of preparation If substitute, powder or liquid Milk (% fat) Fat in preparation (kind) and amount	Cheese, vegetables, meat, etc.	vol; egg equivalent

Food Group:	Did You Specify:	Did You Probe for Additions and Amounts of:	Preferred Serving Size Measure:
Desserts, Baked Goods			
Puddings, Custards	Low-cal or regular Mix or scratch Milk (% fat) With or without egg	Topping	vol
Cookies	Kind (i.e., sandwich, wafer, etc.) Flavor Brand Ingredient fat	Nuts Icing Creme filling	sm, med, or lg
Cakes	Kind Layer, sheet or cupcake Ingredient fat, additional oil	Frosting, filling, topping (Specify kind)	cube; wedge
Pies	Kind (filling) Single or double crust Ingredient fat for filling and crust	Topping	wedge; portion of whole
Shortcake	Specify type of fruit Specify type of cake (i.e., biscuit, sponge, etc.)	Topping	cube; wedge; diameter
Cobbler	Specify type of fruit Specify type of crust (i.e., crumble, biscuit, pie, etc.)	Topping	cube; vol
Gelatin Desserts	Low-cal or regular	Topping, other additions (fruit, etc.)	vol
Fats			
Oil, Shortening	Brand and/or type of fat		vol
Salad Dressing	Brand, type (i.e., regular, low-cal, fat-free, etc.) Creamy or clear		vol
Margarine, Butter	Brand or major oil Regular, low-cal, low-fat, fat-free Form (stick, tub, squeeze, whipped, spread)		vol
Cream Cheese	Specify if whipped or solid		vol
Fruits/Fruit Juices	Ready to drink, frozen, or fresh Sweetened or unsweetened Fresh, canned, or dried Syrup (light or heavy), juice, or water packed With or without peel		vol *if fresh fruit, specify sm, med, or lg

Food Group:	Did You Specify:	Did You Probe for Additions and Amounts of:	Preferred Serving Size Measure:
Grain Products			
Bread, Rolls	Kind (white, whole wheat, rye, etc.)	Butter, margarine, other spread	standard size slice *if rolls, specify sm, med, or lg
Breadsticks	Bread or cracker type	Butter, margarine, other spread	LI
French Toast	Egg or egg substitute Fat in preparation Kind of bread Commercial, homemade, frozen	Butter, margarine, syrup, etc.	standard size slice
Sweet Rolls, Doughnuts	Yeast or cake-type Baked or fried (i.e., turnover)	Frosting, glaze, nuts, preserves	dia; sm, med, or lg
Pancakes, Waffles, Biscuits, Muffins	Kind (i.e., whole wheat, buckwheat, bran, etc.) Mix, scratch, commercial, or frozen Fat in preparation (kind)	Butter, margarine, syrup, etc. Topping (i.e., fruit, nuts, etc.)	dia
Cereal, Granola	Kind, Brand If hot cereal, fat in preparation, made with milk or water	Milk (% fat) Sweetener, fat, fruit, etc.	vol *if cooked cereal, specify vol BC or AC
Pasta, Rice	Kind (i.e., spaghetti, spinach, egg, brown, etc.) Fat in preparation (kind)	Fat (kind), sauce, cheese, etc.	vol, specify BC or AC
Crackers	Kind, Brand	Spread	number if standard size; sm, med, or lg
Tortilla	Corn or flour Fat used if fried Ingredient fat for homemade tortillas Preparation method: plain or fried	Filling Fat added at the table	dia
Gravies, Sauces	Kind (i.e., beef, chicken, pork, etc.) Mix or scratch Made with milk (% fat) or water Fat (i.e., meat drippings)		vol
Meat, Poultry, Fish			
Meat	Kind, cut Trimmed or untrimmed, % fat of hamburger or type of ground beef (i.e., ground chuck) Fat in preparation (kind) Visible fat eaten Marinade Breaded or battered and fried Fresh or cured Preparation method If hamburger, drained or rinsed	Sauce, gravy, etc. If breaded, was the coating eaten?	cube; wt * if wt, specify BC or AC, w/ or w/o bone

Food Group:	Did You Specify:	Did You Probe for Additions and Amounts of:	Preferred Serving Size Measure:
Meat, Poultry, Fish (Cont.)			
Meatloaf, Meatballs	Kind, % fat or type of meat (i.e., ground round) Fat in preparation (kind)	Sauce, gravy, etc.	cube; wt * if wt, specify BC or AC *if meatballs, specify diameter
Poultry	Light, dark, or mixture of meat Name of part Skin eaten or not Breaded or battered and fried Fat in preparation (kind) Marinade Preparation method	Sauce, gravy, etc. If breaded, was the coating eaten?	wt; sm, med, or lg piece * if wt, specify BC or AC, w/ or w/o bone
Fish	Kind Breaded or battered and fried Fat in preparation (kind) Fresh, canned, or frozen If canned, water or oil pack; drained, undrained, or rinsed Marinade Preparation method	Sauce, etc. If breaded, was the coating eaten?	cube; wt; vol * if wt, specify BC or AC, w/ or w/o bone
Bacon	Specify type (i.e., beef, pork)		number of slices
Cold Cuts, Luncheon Meats	Kind, % fat, brand		wt
Meat Substitutes			
Tofu	Firm or regular		vol
Mixed Dishes	Mix, scratch, or commercial Fat in preparation (kind) Meat, kind, and % fat Sauce or gravy (type) Milk or cheese (% fat or kind) Pasta or vegetables If Chow Mein, with or without noodles, noodles fried or soft	Topping (i.e., croutons, crackers, cheese, etc.)	vol
Frozen Entrees	Brand Complete name of entree		wt of pkg and portion of pkg eaten
Pizza	Deep dish, thick, or thin crust Restaurant, fast food, package, or homemade Brand Specify type (i.e., pepperoni, cheese only, vegetarian, etc.)	Topping, extra cheese	wedge; portion of whole
Restaurant Meals	Name of restaurant if fast food Name of menu item Method of preparation Price range of restaurant	Additions at the table With or without cheese	*if fast food, portion of standard size order

Food Group:	Did You Specify:	Did You Probe for Additions and Amounts of:	Preferred Serving Size Measure:
Seasonings/Condiments	Jelly (specify type) Pickle, relish, catsup, mustard, steak sauce, etc.		vol
Snacks			
Candy	Kind, brand Filling (type)	Nuts	number if standard size pieces
Popcorn	Commercial, home popped, or microwave Brand, flavor If light, indicate if for salt, fat, or both Fat in preparation (type) Amount in cups	Topping (i.e., cheese, fat [type], etc.)	vol; wt of pkg and portion of pkg eaten
Potato Chips	Thick or Thin type		vol; number eaten; wt of package and portion eaten
Nuts	Type Raw or roasted If roasted, oil or dry		vol; number * if vol, indicate if shelled or unshelled
Soups	Ready to serve, diluted, undiluted Milk (% fat) or cream added Chunky or regular Noodles or pasta Specify if low-fat Meat (kind)	Croutons, crackers, cheese, etc.	vol; wt of can
Vegetables	Method of preparation Fresh, frozen or canned Fat in preparation (kind)	Fat (kind), cheese, sauce, nuts, dip, etc.	vol, specify if cooked or raw
Salads	Kind (major vegetables) Lettuce (type) If potato or tuna, with or without egg If potato or coleslaw, mayonnaise or vinegar dressing	Dressing, kind and/or brand Croutons, seeds, etc.	vol
Baked Potato	Skin eaten or not	Butter, sour cream, etc.	sm, med, or lg; LI
French Fries	Frozen, fresh, restaurant	Catsup, other condiments	vol; number and thickness (i.e., shoestring, steak) * if fast food, size of order (sm, med, or lg) and portion of order eaten

Record portion sizes in the following standard measurements:

Weight (wt) in grams (gm) or ounces (OZ)
Volume (vol) in fluid ounces (FO), cups (CP), tablespoons (TB), or teaspoons (tsp)
Fraction of the whole (i.e., 1/8 of 9" pie)
Size: Small (sm), Medium (med) or Large (lg) for food items such as fresh fruit, potatoes, chicken breast.

Record dimensions for the following shapes:

Label and verify all dimensions. Write "DV" (documentor verified) for very large or very small portions.

Shape	Measurement Needed	Example
Sphere	Diameter (dia)	Meatball, 3" dia
Cylinder or disk	Diameter (dia) x thickness (th)	Meat patty, 4" dia x 1/2" th
Rectangle or cube	Length (L) x height (H) x width (W)	Lasagna, 3" L x 2" W x 1" H
Wedge	Length (L) x height (H) x width of arc (arc)	Layer cake, 4" L x 3" H x 2" arc

APPROVED ABBREVIATIONS
Use these and other standard abbreviations when documenting food intake on *Four-Day Food Records*.

AC - after cooking	H - height	RTE - ready to eat
amt - amount	hyd - hydrogenated	s - saturated
approx - approximate	L - length	sl - slice
avg - average	LC - low calorie	sm - small
BC - before cooking	LF - low-fat	swt - sweetened
brd - breaded	lg - large	TB - tablespoon
cnd - canned	LI - linear inch	tsp - teaspoon
choc - chocolate	mayo - mayonnaise	th - thickness
chpd - chopped	med - medium	TVP - textured vegetable protein
ckd - cooked	misc - miscellaneous	ukn - unknown
comm - commercial	NA - nothing added	veg - vegetable
crax - cracker	NFS - not further specified	vol - volume
CP - cup	NVF - no visible fat	W - width
dia - diameter	OZ - ounce	w/ - with
DV - documentor verified	pkg - package	wt - weight
FF - fat free	pc - piece	w/o - without
FO - fluid ounces	prep - prepared	
gm - gram	poly - polyunsaturated	
gr - ground	RTD - ready to drink	

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Figure 10.2
Guidelines for Documenting the Fat Added Columns of the 4DFR

How to Use the Fat Added Columns

It is very important that the *4DFR* include all sources of fat consumed by the participant. Two of the major sources of fat in the diet are in food preparation and as additions to food at the table. For this reason, two columns are on the documentor's page of the *4DFR*. One column asks, "Was fat added in preparation?," and the other column asks, "Was fat added at the table?" The purpose of these columns is to remind the documentor to ask the participant these questions for foods that commonly contain fat or have fat added to them.

Use these columns to document fat only (e.g., oil, shortening, salad dressing, margarine, butter, mayonnaise, etc.) added to foods, and ingredient fat in foods (e.g., butter in cookies). It is appropriate to leave both columns blank for foods that DO NOT typically have fat added to them (e.g., catsup, jelly, carbonated beverages, fresh fruits, and juices, etc.)

Follow the steps listed below as the *4DFR* is documented with the participant. Use the examples provided for each column to assist you.

Column 1: Was fat added in preparation?

Ask the participant if fat was added in the preparation of food items.

- Enter the participant's answer in the "Was fat added in preparation?" column. Write a **Y** in the column if the answer is yes, an **N** for no, and a **U** for unknown.
- If a participant knows the item was prepared with fat, write the type and amount of fat on the documentor's line for that food item.
- Ask the participant if the amount of fat was for her portion only. If it was not for her portion only, write the total amount prepared or adjust the amount to match her portion accordingly.
- For most commercial products the type and amount of fat will be unknown, therefore, do not mark the column for these products.
- For fat free commercial products, write "fat free" as a description for the item and do not mark in the column.

Column 2: Was fat added at the table?

Ask the participant if fat was added to the food at the table or prior to eating.

- Enter the participant's answer in the "Was fat added at the table?" column. Write a **Y** in the column if the answer is yes, an **N** for no, and a **U** for unknown.
- If a participant added fat, write the type and amount of fat on the documentor's line for that food item.
- If the participant wrote the added fat on a separate line, write a **Y** in the column titled "Was fat added at the table?," and draw an arrow to the line where the fat is written.
- Ask the participant if the amount of fat was for her portion only. If it was not for her portion only, write the total amount prepared or adjust the amount to match her portion accordingly.

Figure 10.2. (Continued)

Place Prepared H = Home R = Restaurant O = Other		Day: _____ Date: ____/____/____		
Meal B = B'fast L = Lunch D = Dinner S = Snacks	↓			
↓		↓	Foods And Beverages	Amount
1	B	H	Oatmeal	1 cup
2	L	H	Black-eyed peas	1/2 cup
3	D	H	Kraft Macaroni and Cheese	1 cup
4	D	H	Broiled Chicken Breast	1 med.
5	L	H	Carrots, boiled	1/2 cup
6	D	H	Tortilla, homemade flour, steamed	8" diam.
7	S	H	Pie, apple 3"arc X 4"L X 1/2"th	1 piece

Explanation of Examples:

Line 1: Oatmeal, made with butter (1 tsp), no fat added at the table.
Line 2: Black-eyed peas seasoned with ham hocks, ham eaten, no fat added at the table.
Line 3: Macaroni and cheese prepared with margarine (specified on page 5 of 4DFR), and 2% milk, no fat added at the table.
Line 4: Chicken basted with butter (amount unknown), no fat added at the table.
Line 5: Carrots made with olive oil, 1 TB oil for 3 cups carrots, no fat added at the table.
Line 6: Tortillas made with lard, 2 TB for 10 tortillas, no fat added at the table.
Line 7: Pie made with unknown type of shortening and butter in the filling.

Do Not Write On This Page

STOP

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Enter a N = No Y = Yes or U = Unknown for each column.

		Was Fat Added at the Table? ↓	Was Fat Added in Preparation? ↓
1	AC, instant, no flavorings, made with butter (1tsp)	Y	N
2	AC, boiled, frozen, seasoned with ham hocks, ham eaten	Y	N
3	Package mix, made with margarine, 2% milk per pkg. directions	Y	N
4	Skin removed BC, basted with butter (amount unknown)	Y	N
5	AC, sliced, from fresh, with olive oil (1 TB for 3 cups)	Y	N
6	Made with lard (2TB for 10 tortillas)	Y	N
7	Double crust, unk. type or shortening in crust, butter in filling	Y	N

Figure 10.2. (Continued)

Place Prepared H = Home R = Restaurant O = Other	Meal ↓ B = B'fast L = Lunch D = Dinner S = Snacks		Day: _____ Date: ___/___/___	
	↓	↓	**Foods And Beverages**	**Amount**
1	B		Muffin, bran	1 small
2	B		Weight Watchers margarine, tub	1 tsp.
3	D		Carrots, boiled	½ cup
4	D		Baked potato	1 large
5	B		French Toast	2 slices
6	B		Butter, whipped	
7	B		Grits, cooked in milk	½ cup
8	D		Green beans	½ cup

Explanation of Examples:

Line 1: Commercially made muffin, margarine added to muffin.
Line 3: Carrots cooked without fat, 1 tsp. margarine (specified on page 5 of 4DFR) added at the table for her portion of carrots.
Line 4: Potato baked without fat, 2 TB. sour cream added at the table for her potato.

Do Not Write On This Page

STOP

For Clinic Use Only

Enter a N = No Y = Yes or U = Unknown for each column.

		Was Fat Added at the Table?	Was Fat Added in Preparation?
1	Commercial, no topping		Y
2	On muffin		
3	From fresh, AC, sliced, 1 tsp. marg.	N	Y
4	Ate skin, 2TB. sour cream	N	Y
5	Frozen, commercial		Y
6	2 tsp., slice		
7	AC, instant, whole milk, 1tsp. margarine	N	Y
8	Unknown prep., 1 TB. butter	U	Y

Explanation of Examples (cont.):

Line 5: Commercially made French toast, 2 tsp. butter added at the table for each slice.
Line 6: Grits cooked without fat, added 1 tsp. margarine (specified on page 5 of 4DFR) at the table for her portion of grits.
Line 7: Green beans eaten at a restaurant, preparation method unknown, 1 TB butter was added at the table for her green beans.

Figure 10.3
4DFR Screening Checklist

1. Participant ID Number: ___ ___ - ___ ___ - ___ ___ ___ - ___
2. Clinical Center Number: ___ ___

Check all *4DFRs* for the following before sending to NASR for processing:

5. ERROR CODE	6. ITEMS TO BE CHECKED	7. YES	8. NO
1	Participant ID barcode label attached in space indicated on page 40 of *4DFR*.		
2	Participant ID number on all odd numbered pages (7 - 39) of *4DFR* (i.e., write the number, stamp the number, or affix a label to the page).		
3	Assigned dates and days for recording match with those listed by the participant in the *4DFR*. If the participant kept her *4DFR* on days other than those assigned, correct the days and the dates on the front of the book.		
4	The participant completed a minimum of three food record days.		
5	Entire section for Vitamin and Mineral Supplements is complete (*4DFR* page 4). • "Yes" box checked and remainder of page completed if participant took a supplement. • Supplements recorded on the days taken in the daily record. • "No" box checked if participant did not take a supplement.		
6	Entire section for General Questions is complete or verified by documentor (*4DFR* page 5). • Information is complete for each item listed. • Documentor has verified (written NA and initialed) those items that the participant does not use.		
7	Back page of *4DFR* (page 40) completed. • Shaded section complete and data items correctly key-entered. • Intake and Reliability Information complete.		
8	Food labels are in a sealed envelope or clear plastic bag, and stapled to page 39 of the *4DFR*.		
9	Documentor used a different colored pen than the participant.		
10	Documentor is certified to document *4DFRs*.		
11	The *4DFR* is stapled and correctly assembled.		
12	The date peer reviewed is within 3 working days of the date documented.		
13	The 4DFR is mailed to the CCC within 2 weeks of date received at the CC.		

Figure 10.4
Sample of FFQ Error Report

MEMBER:31 10000 A BOOKLET #:00125477 VISIT CODE:1 DATE COMPLETED:
PRINTED:9/30/1993

WHI FFQ ERROR REPORT

ERROR DESCRIPTION	(STARTS ON) PAGE	ITEM DESCRIPTION
INVALID	1	Booklet number can not be read, or pages have different numbers
INVALID	1	Date
BLANK	4	Adjustment 16
TOO MANY BLANK ITEMS	7	MEAT SECTION
ENTIRE ITEM BLANK	7	Shellfish, not fried
ENTIRE ITEM BLANK	7	Mac and Cheese, lasagna, pasta w/
ENTIRE ITEM BLANK	7	Spaghetti or other pasta w/ meat
ENTIRE ITEM BLANK	7	Spaghetti or other pasta w/o meat
ENTIRE ITEM BLANK	7	Low-fat Pizza
ENTIRE ITEM BLANK	7	Pizza
ENTIRE ITEM BLANK	7	Tamales with or without meat
ENTIRE ITEM BLANK	7	Chilaquiles
ENTIRE ITEM BLANK	7	Soft quesadilla
ENTIRE ITEM BLANK	7	Crispy quesadilla and chili relle
ENTIRE ITEM BLANK	7	Soft taco and enchilada baked
ENTIRE ITEM BLANK	7	Faluta and crispy rolled taco
ENTIRE ITEM BLANK	7	Regular burrito and enchilada
ENTIRE ITEM BLANK	7	Taco and tostada
ENTIRE ITEM BLANK	7	Low fat lunch meats
ENTIRE ITEM BLANK	7	Regular lunchmeat
ENTIRE ITEM BLANK	7	Hot dogs, sausage
ENTIRE ITEM BLANK	7	Creamy soups
ENTIRE ITEM BLANK	7	Bean soups
ENTIRE ITEM BLANK	7	Vegetable soups
ENTIRE ITEM BLANK	7	Menudo and tortilla soup
ENTIRE ITEM BLANK	7	Other soups
TOO MANY BLANK ITEMS	10	SWEETS SECTION
ENTIRE ITEM BLANK	10	Low fat dairy desserts
ENTIRE ITEM BLANK	10	Donuts, cakes, pastries
ENTIRE ITEM BLANK	10	Cookies, regular
ENTIRE ITEM BLANK	10	Pumpkin and sweet potato pie
ENTIRE ITEM BLANK	10	Pies, fried pastries, pastelitos
ENTIRE ITEM BLANK	10	Chocolate candy
ENTIRE ITEM BLANK	10	Hard candy, sugars
TOO MANY BLANK ITEMS		WHOLE FFQ

Section 10
Dietary Assessment

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SECTION 11

BLOOD AND URINE COLLECTION, PROCESSING AND SHIPMENT

INTRODUCTION

A fasting blood sample is collected from all participants in the Women's Health Initiative at the first screening visit. All participants in the Clinical Trial (CT) also provide blood samples at their first annual visit and a subsample of participants provide blood samples at three years and every three years thereafter. All Observational Study (OS) participants provide blood samples at their three-year visit.

First-morning urine specimens are collected from all participants recruited at the three designated Clinical Centers (CCs) participating in the bone density substudy (University of Alabama, University of Arizona, and University of Pittsburgh). Participants provide a urine sample during screening, at the first annual visit, the three year visit, and every three years thereafter. (See *Vol. 1, Table 1-A1.1 - Frequency of Data Collection* for schedules of blood and urine collections.)

The CCs send specified serum samples to their local laboratory for specified analyses. The remaining serum, plasma, RBCs, buffy coat, and urine samples are shipped to the central repository, McKesson BioServices in Rockville, MD. McKesson BioServices ships selected samples to the central lab, and other selected labs, for analyses. This section describes procedures for collecting, processing, storing, and shipping blood and urine samples to McKesson BioServices.

11.1 General Guidelines

11.1.1 Safety Procedures - Precautions for Handling Blood

The WHI has adopted the Universal Precautions for blood collection, processing and shipping. These precautions are intended as optimal "guidelines." These do not apply to urine unless there is visible blood in the urine. The term *Universal Precautions* refers to an approach to infectious disease control which assumes that every direct contact with body fluids is infectious. Also refer to the Occupational Safety and Health Administration (OSHA) guidelines which should be available from your institution for handling blood specimens.

Follow all local requirements for handling and disposing of blood and materials exposed to blood. Check with your institution's Health and Safety office for any additional requirements as there may be some local variation at each CC, which may be stricter or slightly less strict than those listed below.

The following are guidelines for all blood collection and processing procedures:

- Handle all blood specimens as potentially infectious material. Transmission of the infectious agents associated with hepatitis and acquired immunodeficiency syndrome (AIDS) via "needle stick" skin punctures have been documented.
- Wear disposable plastic latex gloves when collecting and processing specimens. When drawing blood, change gloves between participants.
- Wear protective eye goggles, a face mask, a full face shield, or work behind a barrier shield at all times when processing blood. Regular glasses without splatter shields are not sufficient.
- Encourage CC staff having direct contact with blood specimens to get a Hepatitis B vaccination. Your local institution may provide Hepatitis B vaccinations for personnel handling blood specimens. The Hepatitis B vaccine provides immunity against Hepatitis B, an infectious, blood-borne disease causing inflammation of the liver with possibly serious or fatal consequences. The vaccination series involves three separate doses over six months. This protection is believed to last five to seven years at which time a booster dose may be needed.
- Wash your hands with soap and water:
  - Immediately after contact with blood or other infectious materials (even if you wore gloves).
  - Before and after using restroom facilities.
  - After you take off your gloves or other protective clothing.
  - Before and after each participant contact.
  - When you leave the work area where blood or other infectious materials are present.
- Do not use gloves if they are peeling, cracked or discolored, or if they have punctures, tears or other evidence of deterioration. Cover skin cuts or abrasions with a Band-Aid underneath the glove.
- Anyone performing a process where there is a potential for splashing of blood (e.g., the processing of blood) should wear a long-sleeved, buttoned-up, fluid-resistant lab coat.
- Use disposable lab coats, if available. Place disposable protective equipment in a labeled infectious waste container for disposal.
- Remove the disposable/non-disposable lab coat when leaving the blood draw area. The lab coat worn in the blood draw area should not be worn in other areas of the clinic.
- Tie back any long hair.
- If you accidentally sustain a contaminated (or used) needle stick, thoroughly cleanse the wound with soap and water. Notify the CC physician to order an analysis of the participant's serum for possible hepatitis

or HIV antibodies. Complete a local accident report, as needed, and follow all appropriate OSHA guidelines as dictated by your institution.

- Do not manipulate needles, scalpel blades, or other contaminated sharp objects by hand. Do not bend, break or remove needles from disposable syringes by hand. Store unused needles in a secure cabinet when the CC is closed.
- Do not recap or re-sheath needles or sharp instruments unless absolutely necessary. If you need to recap a needle, cover it immediately after use. To recap the needle, use a cap holder designed for this purpose (placed in close proximity); or use a hemostat. Do not use your hand to recap the needle since this is the most common cause of sustaining a contaminated needle stick.
- Use 0.1% sodium hypochlorite (10% household bleach) to clean up any spills of blood, serum or urine. Use this solution on all work surfaces at the end of each day. Dilute one part household bleach with nine parts water to get a 0.1% sodium hypochlorite solution. Apply with a paper towel. Do not use an aerosol spray to apply the solution.
- Deposit all used needles, blood collection tubes, transfer pipettes and pipette tips in puncture-resistant containers for safe disposal.
- Place all other used blood processing supplies and blood products in biohazard bags for disposal. Also dispose of other materials exposed to blood in biohazard bags.
- Never perform any pipetting by mouth, especially if any blood or serum is involved.
- Avoid formation of potentially infectious aerosols by carefully removing stoppers from the vacutainer tubes and by careful pipetting and centrifugation.
- Never allow food or drink in the blood drawing or processing rooms. Do not store food or drink in the same refrigerator or freezer as blood samples.
- Do not eat, drink, apply cosmetics or lip balm, or handle contact lenses in work areas where blood or potentially infectious materials are present.
- Assume all laundry to be contaminated. Wear protective gloves when handling laundry. Bag laundry at the location where it was used. Double bag if soaking through is likely.
- Label all containers of infectious waste (i.e., biohazardous and medical waste), refrigerators and freezers containing blood or other potentially infectious materials with the biohazard symbol. The biohazard symbol must be black on an orange background.
- Transport all specimens or containers of blood and other potentially infectious materials in a secondary container (e.g., plastic bag or other container having a liquid-tight seal).

11.1.2 Training and Certification (Required)

A CC staff person may draw, process and ship the blood and urine specimens after completing the WHI training and certification process. Such a staff person must become familiar with *Section 11 - Blood and Urine Collection, Processing and Shipment* and should also be familiar with local or state certification requirements. Keep a copy of any local and state requirements relating to the collection and processing of blood and urine products on file at the CC.

Because blood collection may involve a small amount of pain for the participant, it is important that phlebotomists review the techniques involved in the collection process. Phlebotomists should be highly experienced with vacutainer and butterfly blood collections, prepared to handle common problems such as fainting, and familiar with precautions to avoid exposing themselves to blood. Ideally they will be CPR certified. They should: 1) read "Collection and Handling of Laboratory Specimens: A Practical Guide" or similar phlebotomy manual; 2) wear clean white lab coats (with no blood stains) and appear generally neat and tidy; 3) wear name tags and introduce themselves to the participants before the blood draw; and 4) not chew gum or have any food items in their mouths during blood draws.

Because the study depends on the voluntary return of participants over an extended period, the phlebotomist should make every effort to make the entire procedure as easy and painless as possible. The phlebotomist should remain calm and project an attitude of competence even when faced with the most nervous or inquiring participant. The best way to achieve this is to be thoroughly knowledgeable about all aspects of the procedures. This includes knowledge about the participant contact, the handling of each tube and the purpose of each sample.

11.1.3 Facilities

Phlebotomy Room

Perform blood draws in a private area such as an isolated room (blood drawing room) or in an area separated by room dividers. Equip the room with all the necessary blood drawing supplies. Use a counter or work table for all of the blood handling equipment and supplies. The blood drawing room should be clean and tidy with no obvious evidence of a previous blood draw such as used needles, blood stains, etc. A phlebotomy chair should be available for 15 to 20 minute periods to allow participants to be seated for a few minutes before the blood draw. Ideally, only the participant and phlebotomist should be in the room during the procedure.

Blood Processing Room

Equip the blood processing room with a refrigerated centrifuge, a small refrigerator and sufficient counter space for the processing of blood specimens. A -70°C freezer should be in or near the room. The room must have a sink and running water available. Use one counter area for processing the blood samples and another counter area for completing paperwork. Safety regulations state food and drink should not be kept in refrigerators or freezers in which you put the blood samples. Food should not be kept in the blood processing room even if it is not in the same refrigerator as the blood samples. Food should not be eaten in the blood processing room.

11.1.4 Equipment and Supplies (Required)

See *Section 2.3 - Equipment and Supplies* for lists of required and recommended blood collection, processing and shipment supplies. Orders for cryovials, labels and shipping supplies are filled by McKesson BioServices. Clinical Centers also have the option of ordering the three blood collection tubes from McKesson BioServices. Clinical Centers can order blood collection tubes using the Notification of WHI Shipment form. If your local or state laws require different or additional shipment supplies, contact McKesson BioServices to see if they can provide the supplies for you. When vendors change or update their catalogs, check the part numbers to be sure you are ordering the correct tubes. Some vendors have changed part numbers in the past. When receiving the royal blue-stoppered tubes, check to be sure that the "7 ml" is printed in **red** on the tube label, indicating a serum tube with no anticoagulant. A tube with green "7 ml" printed on the label indicates the tube contains heparin. Try to maintain at least a 2-month inventory of blood drawing and processing supplies. When purchasing blood collection tubes from a vendor and not ordering from McKesson, specify the expiration date so the vendor does not send you its older stock.

Calculate the quantities of disposable supplies needed based on your CC's projected workload. Allow sufficient time for the delivery of the required supplies from the vendors.

Local preferences, procedures and regulations may require a CC to have access to items that are not on the list.

11.2 Blood Collection

11.2.1 Blood Sample Labels (Required)

McKesson BioServices provides blood sample label sets with a unique 6-digit preprinted number and corresponding barcodes to use during the collection and processing of blood samples. The labels are specifically made for use in low temperature freezers. Clinical Centers use the labels from one label set to label the blood collection tubes, blood collection form, and all cryovials for one blood draw. The label on *Form 100 - Blood Collection and Processing* links the blood sample number to the participant ID and information about the blood draw such as date and time drawn.

Use one set of blood sample labels for each blood sample collected and recorded on *Form 100 - Blood Collection and Processing*. For example, one set of multiple blood sample tubes collected at one time from a participant have the same blood sample number. Blood samples collected from a participant at different times or different visits have unique blood sample numbers. Blood collected on different days or different times (> 1 hour apart) are considered different draws and require two separate Form 100s with different blood sample numbers.

Each set of blood sample labels contains the following labels, each printed with the unique 6-digit blood sample number:

- Two labels for *Form 100 - Blood Collection and Processing*, one for the front of the form and one for the back of the form. Each label also contains a barcode label corresponding to the 6-digit blood sample number and the words "Blood Form." The blood processor uses the back of the form for recording blood processing data; and the label on the back of the form assists the blood processor in properly identifying the blood sample during processing.
- Seven labels for the blood collection tubes, printed "Tube" on each of the seven labels.
- Thirteen labels for the 13 cryovials. (*Note:* Two cryovials [-01 and -15] were previously discontinued and one [-20] was added beginning 12-1-95.) Each of the thirteen labels contains the 6-digit blood sample number, a 1-letter check digit or a 2-digit cryovial number, and a corresponding barcode. The 6-digit blood sample number uniquely identifies each blood sample and the 2-digit cryovial number uniquely identifies each cryovial. Placing the blood sample number on a participant's *Form 100* identifies the blood sample as belonging to that participant. Each label also gives the color of the blood collection tube stopper and the type of the aliquot specimen. (You may use local labels for the triglyceride and CBC samples you send to your local lab.)

  Beginning October 1, 1995, the buffy coat for cryovial - 20 is collected from the two light blue vacutainer tubes. The wording on the label was changed from "lavender" to "light blue".

Vacutainer Stopper Color	Cryovial Number	Specimen Volume and Type
Royal Blue	02	1.8 ml serum
Royal Blue	03	1.8 ml serum
Royal Blue	04	1.8 ml serum
Royal Blue	05	1.8 ml serum
Light Blue	06	1.8 ml citrate plasma
Light Blue	07	1.8 ml citrate plasma
Light Blue	08	1.8 ml citrate plasma
Royal Blue	09	Triglyceride, serum
Lavender (10 ml)	10	1.8 ml EDTA plasma
Lavender (10 ml)	11	1.8 ml EDTA plasma
Lavender (10 ml)	12	1.8 ml EDTA plasma
Lavender (10 ml)	13	Buffy Coat
Lavender (10 ml)	14	1.8 ml RBC
Lavender (2 ml)	16	CBC
Light Blue	20	Buffy Coat

Figure 11.1

Blood Sample Labels

[BARCODE] 123456 A Blood Form	[BARCODE] 123456 A Blood Form	123456 A Tube
123456 A Tube	123456 A Tube	123456 A Tube
123456 A Tube	123456 A Tube	123456 A Tube
[BARCODE] 123456-02 Royal blue tube, serum orange cap	[BARCODE] 123456-03 Royal blue tube, serum orange cap	[BARCODE] 123456-04 Royal blue tube, serum orange cap
[BARCODE] 123456-05 Royal blue tube, serum orange cap	[BARCODE]] 123456-06 Light blue tube, plasma blue cap	[BARCODE]] 123456-07 Light blue tube, plasma blue cap
[BARCODE]] 123456-08 Light blue tube, plasma blue cap	123456-09 Royal blue tube, triglyceride, serum	[BARCODE] 123456-10 Lavender tube, plasma yellow cap
[BARCODE] 123456-11 Lavender tube, plasma yellow cap	[BARCODE] 123456-12 Lavender tube, plasma yellow cap	[BARCODE] 123456-13 Lavender tube, Buffy coat white cap
[BARCODE] 123456-14 Lavender tube, RBC red cap	123456-16 2 ml Lavender, CBC	[BARCODE] 123456-20 Light blue tube, Buffy coat white cap

11.2.2 Identification of Participants Requiring Blood Collection

11.2.2.1 Routine Visits

First Screening Visit: Collect a fasting blood sample from all participants at SV1 if they have been fasting for at least 12 hours. This includes participants interested in the CT components and participants interested in the OS.

Clinical Centers have the option to collect blood samples on participants at the Screening Visit 2 (SV2) if this fits better with their clinic flow. They may also schedule a time separate from the visit. For example, a CC may schedule SV1s and SV2s in the afternoon and not require participants to be fasting; then ask the participants to come for blood draws in the morning on a different day. If a woman has not been fasting for at least 12 hours at SV1, postpone the blood draw until SV2 and ask the woman to fast at least 12 hours before the next visit.

Perform any off-site blood draws using the same procedures as those performed at a primary clinic, including adherence to time limits and equipment for processing and freezing. See *Figure 11.3 - Guidelines for Blood Processing* for a summary of time requirements.

Follow-up Visits: The schedule of blood collection for the CT and OS is different. In addition, the women in the CT blood draw subsample are determined at the time of randomization. See *Vol. 1, Table 1-A1.1 - Frequency of Data Collection* for the schedule of blood collection and

Figure **11.2** – *Blood Collection and Aliquot Schedule* for tubes to collect at the indicated contacts.

Figure 11.2
Blood Collection and Aliquot Schedule

Blood Collection Tube		Three 7 ml Royal Blue		Two 4.5 ml Light Blue		One 10 ml Lavender			One 2 ml Lavender
Cryovials		Four 1.8 ml Serum	Trig. 0.5 ml Serum	Coag Panel Three 1.8 ml Plasma	One 1.8 Buffy coat	Lipid Panel Three 1.8 ml Plasma	One 1.8 RBC	One 1.8 Buffy Coat	WBC, Hct platelet count
Study	Visit								
CT/OS	SV1	X	Hrt if Lipemic	X	X	X	X	X	X
CT	1st Annual	X	Hrt if Lipemic	X	X	X	X	X	
CT	Subsample at 3rd, 6th, and 9th Annual	X	Hrt if Lipemic	X		X			
OS	3 Year	X		X	X	X	X	X	X

11.2.2.2 Quality Assurance (QA) Samples

There are no QA blood samples to collect.

11.2.3 Volume of Blood to Collect (Required)

The volume of blood to collect depends on the type of visit.

The volume of blood to collect depends on the type of visit. *Figure 11.2 – Blood Collection and Aliquot Schedule* shows the number and type of vacutainer tubes to use at the SV1 and subsequent annual visits.

11.2.3.1 Blood Sample for the Local Lab (Required)

The analyses you request from your local lab depends on the type of visit and test needed to determine the woman's eligibility. See *Figure 11.2 – Blood Collection and Aliquot Schedule* for a summary.

At SV1:

- Collect blood for analyses of hematocrit and platelet count to be used to determine the participant's eligibility and for analysis of WBC. (Be sure to ask the lab to give a platelet count and not a platelet estimate.) As of March, 1996, hemoglobin is no longer a criterion for eligibility and is no longer required.
- If the woman is interested in HRT and her serum is lipemic, send an aliquot of serum from the royal blue tube for a triglyceride level. See *Section 11.3.3.1 - Preparation of Blood Cryovials (Required)* for details of determining lipemia.

At Year 3 for OS participants:

- Collect blood for analysis of WBC, hematocrit, and platelet count.

11.2.3.2 Routine Blood Sample for the Serum Repository (Required)

Send aliquoted cryovials to McKesson BioServices according to the schedule shown in

Figure **11.2** *– Blood Collection and Aliquot Schedule.* Collect approximately 42 ml of blood using royal blue, light blue, and lavender-stoppered tubes.

11.2.4 Preparation for Blood Collection

11.2.4.1 General Instructions for Participants Before Blood Draws (Required)

Before visits at which you will be drawing blood, tell each woman to prepare for the blood collection. Ask her to:

1. Fast (that is, take nothing by mouth except water) for at least 12 hours before all blood collections. To reduce the likelihood of fainting, encourage her not to initiate the fast much more than 16 hours before the blood draw. Also ask her to drink water liberally during the fasting period to prevent dehydration and reduce the likelihood of fainting.
2. Take all regular medications except for insulin or oral medication used to control diabetes. (Note that participants with diabetes may have more specific guidelines from their primary physician about blood draws.)
3. Take no aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) for 48 hours before the visit. NSAIDs that are taken regularly may be continued and taken within the 48 hours before the blood draw, consistent with the participant's usual schedule.
4. Do not smoke for at least one hour before the blood draw.
5. Perform no vigorous physical activity (such as jogging or bicycling) for at least 8 hours before the blood draw.
6. Wear clothing which allows the sleeve to be easily raised above the elbow without constricting the blood flow to forearm and hands.

11.2.4.2 Directions for Staff When Participants Do Not Follow Instructions (Required)

1. In general, do not draw the blood sample if the participant is not fasting. To be fasting the participant should not have consumed even a lifesaver, stick of gum or other sugar-containing food items during the pasting period, or has "accidentally" ingested a sip of juice, black coffee, tea, single bite of other food items, or any amount of alcohol.

   For safety reasons, a participant with diabetes should be scheduled as the first draw of the day. If a participant with diabetes cannot delay taking her diabetic medications until after the blood draw, you may draw her blood even if she has recently taken the medications.

   - If a participant has taken her diabetic medication or advises you that she is not fasting, reschedule the blood draw when fasting will be convenient for the participant, if she is willing to return to the CC. Do not coerce the participant to return to the CC for a blood draw.
   - If she is fasting but took her diabetic medication, note that she took the medication in the comments section of *Form 100 - Blood Collection and Processing*.
   - If she is not fasting and is not willing to return to the CC, you may draw the blood, being sure to record on the *Form 100 - Blood Collection* when she last ate. (See Step 1 in *Section 11.2.4.2 - Directions for Staff When participants Do Not Follow Instructions*.)

   If the participant failed to initiate the fast slightly less than 12 hours before the blood draw, try to do other visit procedures first or delay the blood draw until 12 hours have passed; otherwise, reschedule the blood draw. If 12 hours will not pass before the end of the visit, ask her to come back at another time when she can fast.

   Reschedule the blood draw for another date. (See Step 3 in *Section 11.2.4.5 – Participant Preparation.*) Do not coerce the participant to return to the CC for a blood draw – her adherence and retention in the study overall is more important than obtaining a fasting blood sample. In the rare circumstances where the participant is not fasting and is unable or unwilling to return to the CC, you may draw the blood, being sure to record on *Form 100 – Blood Collection and Processing* when she last ate.

2. If a woman has smoked during the hour before the blood draw, try to do other visit procedures first until an hour has passed since her last cigarette. If postponing the draw is not possible, proceed with the draw.
3. If a woman has done vigorous activity within eight hours of the blood draw, try to do other visit procedures until eight hours have passed since the exercise session. If the activity was quite recent, schedule the blood draw for another time. "Non-vigorous" physical activities include walking/jogging at less than four m.p.h. or stair climbing. Aerobics should be avoided. "Vigorous" activities include vigorous jogging or running. If the participant has indicated she has engaged in vigorous activity within 8 hours prior to her blood draws, indicate this on *Form 100 – Blood Collection and Processing*, and procedure with the blood draw.
4. If the woman's sleeve constricts the arm when rolled or pushed such that it functions as a tourniquet, ask her to remove the blouse or top and offer her a gown.
5. If the participant has indicated she has taken non-routine, non-regular aspirin or non-steroidal anti-inflammatory agents within the 48 hours prior to her blood draw, indicate this on *Form 100 - Blood Collection and Processing* and proceed with the blood draw.

11.2.4.3 Preparation Before the Visit

After the determination has been made that a participant will have a blood draw at the visit:

1. Ensure the blood drawing and blood processing areas are equipped with the proper supplies.
2. Obtain *Form 100 - Blood Collection and Processing* and a blood sample label set.
3. Apply a label with the participant's name and ID number on the form.

4. Indicate the type of visit on *Form 100 - Blood Collection and Processing*.
5. Insert the labeled *Form 100 - Blood Collection and Processing* and label set into the participant's file.

11.2.4.4 Preparation at the Visit (Required)

1. Review the Blood Request part of *Form 100 - Blood Collection and Processing* to see the type and number of tubes of blood to collect.
2. Arrange the set of tubes in a test tube rack, one rack per participant. For the first blood draw occasion, draw the tubes in the order listed below. Attempt to draw the full set of blood collection tubes as described in *Section 11.2.4.4 - Preparation at the Visit* with the tube for CBC last. If you do not draw enough sample on the first occasion, attempt a blood draw on a second occasion. At this second occasion, draw the blood samples you need for eligibility, drawing a small (2 ml) lavender tube for the CBC tube and, for HRT participants only, a royal blue tube for evaluation of triglycerides if the blood is lipemic.

Three	7 ml	Royal Blue
One	2 ml	Lavender (for CBC)
Two	4.5 ml	Light Blue
One	10 ml	Lavender

The order for filling the tubes (Royal Blue - CBC - Light Blue - Lavender) is based on the following:

Royal blue tube first: This tube is trace-element free. You draw this first to avoid the possibility of the anticoagulant in the other tubes (sodium citrate in the light blue tube and EDTA in the lavender tube) contaminating the blood in this tube via the blood or needle.

Lavender (CBC) tube: This tube is for the local CBC. You can draw this tube next to assure you obtain the CBC results needed for eligibility.

Light blue tube: This tube collects plasma for coagulation tests. You do not draw this first to avoid contamination with tissue thromboplastin response to the needle stick, which can affect the coagulation test results. If you do not need to draw the royal blue-stoppered tube, draw a small amount of blood into another royal blue tube to flush the tissue thromboplastin from the needle (you may use a less expensive red-stoppered tube if available at your CC), discard, and then draw the light blue tube for processing.

3. Prepare aluminum sleeves for the royal blue-stoppered tubes. Serum from this tube will be analyzed for carotenoids, which break down in white light. The aluminum foil cover will help protect the blood from light and prevent deterioration of the carotenoids.
4. Check the identifying information on the form and the labels to make sure the form is correctly labeled.

11.2.4.5 Participant Preparation (Required)

1. Blood drawing is standardized to the sitting position. Whenever possible, have the participant in the sitting position for five minutes immediately before venipuncture. Pulse and blood pressure measurements should be performed before the blood draw or an appropriate time thereafter (i.e., wait 30 minutes) in the **opposite** arm.
2. Each participant must sign the Initial consent authorizing the CC to draw blood at the visit before you can draw her blood. Ensure the participant understands the specifics of the blood collection as detailed in the informed consent:
   - Approximately 3 tablespoons of blood will be drawn for CBC and other chemistry tests at baseline.
   - Blood will be drawn at selected follow-up visits to the CC.

- A small risk is associated with the drawing of blood, no greater than if it were performed in a doctor's office.
- A little discomfort may be experienced as the blood-drawing needle penetrates the skin.
- A bruise may develop at the blood-drawing site, however, keeping pressure on the site for 1-2 minutes after the needle is removed may prevent a bruise.
- Very rarely, an infection may develop in the arm as a result of blood drawing

3. Review the blood collection checklist on *Form 100 – Blood Collection and Processing* with the participant. See *Section 11.2.4. – General Instructions for Participants Before Blood Draws (Required)* and *Section 11.2.4.2 – Directions for Staff When Participants Do Not Follow Instructions (Required)*.
   - Ask the participant if she is fasting. The minimum fasting time for the participant is 12 hours. Only water is acceptable to have during the fasting period.
   - Ask the participant if she has engaged in vigorous physical activity in the last 8 hours.
   - Ask the participant if she has taken aspirin or anti-inflammatory agents in the last 48 hours.
4. Review safety issues with the participant.
   - Ask the participant whether she bleeds or bruises easily. If she has had any problems with excessive bleeding or bruising at a venipuncture site, draw her blood only if approved by a Clinic Manager, CC physician or Principal Investigator (PI).
   - Ask the participant if she has ever been told she has a disorder related to blood clotting or coagulation or is taking any anticoagulants or aspirin. Continued bleeding may be a complication if the participant has any problems related to blood clotting or coagulation. To prevent bleeding and preserve the vein, you may need to apply pressure to the site for an extended period of time after you draw the blood. Stay with the participant to ensure the bleeding has stopped. Use Coban self-adherent wrap, or the equivalent, to keep in place for 10-15 minutes over the blood draw site.
   - Ask the participant if she has ever experienced fainting spells while having blood drawn. If she has experienced fainting spells during venipuncture, ask her the frequency of fainting spells. Proceed with the venipuncture if she has fainted only once before. If she advises that she frequently faints, consult the Clinic Manager, CC physician or PI before attempting the venipuncture. Provide smelling salts, amyl nitrate, basin, or cold cloth, if needed. Have orange juice or fruit juice available to offer to the participant. It is advisable to have the participant lie down initially. Note the condition in the participant's file, and perform future blood draws while she is lying down. It is also advisable to loosen any tight clothing before drawing the blood, especially clothing around the neck. (See also *Section 11.2.6.4 - Fainting*.)

11.2.4.6 Handling Participants Who Are Extremely Apprehensive About Having Blood Drawn

Even though blood drawing is standardized for the sitting position, you may ask an extremely apprehensive participant to lie down, if there is a bed available in the CC.

Do not force the participant to have blood drawn under any circumstances. It may help to explain to the participant that the blood drawing is designed to be as painless as possible. Sometimes it helps to let the participant go on with another part of the visit. It may also be helpful to have the participant relax in the blood drawing chair just so that you can check the veins in her arms, without actually drawing blood. If the participant has "good veins" you can reassuringly say, "Oh, you have good veins; there should be no problem." You may also consider using a butterfly needle to perform the draw if the participant is apprehensive. The butterfly needle is a thinner, smaller needle and may be less painful to the participant.

Have the participant sit upright with jacket or sweater removed and with the sleeves rolled up to expose the antecubital fossa (elbow).

Give the participant enough time to feel comfortable both before and after the blood collection. In many cases the most memorable part of the experience for the participant is the blood collection process, the contact with the staff person who draws the blood, and the staff person's general attitude and competence.

This study requires the voluntary cooperation of the participants over a period of many years. Thus, the whole experience must be made as pleasant as possible. Reassure participants who are concerned about the volume of blood that the total amount of blood drawn is about three tablespoons. Also assure the participants that they donate up to 10 times as much blood (450 ml) when they donate a pint of blood.

11.2.5 Venipuncture

11.2.5.1 Wash Hands and Put on Gloves

Wash you hands with soap and water before every blood draw and put on pair of disposable plastic latex gloves.

11.2.5.2 Assemble the Vacutainer Holder

1. Attach the needle to the vacutainer holder.
2. Place the royal blue-stoppered tube in the vacutainer holder being careful not to break the vacuum

11.2.5.3 Identify Venipuncture Site

1. Position the participant's arm on the drawing table. Extend the arm toward you, palm up. Use a padded cushion under her elbow for comfort, if appropriate.
2. Wrap the tourniquet around the arm three to four inches (7.5 to 10.0 cm) above the venipuncture site.

   A tourniquet is used to increase venous filling. It makes the veins more prominent and easier to enter. PRECAUTIONS WHEN USING A TOURNIQUET: The tourniquet should be on the arm for the shortest time possible. **Never** leave the tourniquet on for longer than one (1) minute at a time. To do so may result in hemoconcentration or a variation in blood test values. (It was documented [Clinical Chemistry, 20:1513-1519, 1974] that changes in venous occlusion from 1 to 3 minutes led to a change in various blood components including increase in total lipids (4.7%) and cholesterol (5.1%) and decrease in other components.) If you must apply a tourniquet for the preliminary vein selection, release and reapply it after a wait of one minute. If the participant has a skin problem, put the tourniquet over the participant's shirt or use a piece of gauze or paper tissue so as not to pinch the skin.
3. Ask the participant to make a fist.
4. Identify a vein. Use the antecubital site of either arm as first choice. The median cubital vein is the one used most frequently. If the venipuncture of this vein is unsuccessful, use the cephalic and basilic veins as the next appropriate choices, followed by veins on the back of the hand. Palpate and trace the path of veins several times with the index or middle finger. Unlike veins, arteries pulsate, are more elastic and have a thick wall. Thrombosed veins lack resilience, feel cord-like and roll easily. If you cannot readily see superficial veins, ask the participant to open and close her fist. Lowering the lower arm over the arm of the chair will allow the veins to fill to capacity. Identify the best available vein.
5. Palpate the vein. If you do not feel a vein, try another arm or site (see *Section 11.2.6.3 - Difficult Venipuncture*).
6. Cleanse the vein site with the alcohol prep using a circular motion from the center to the periphery.
7. Allow the area to dry to prevent possible hemolysis of the specimen and a burning sensation to the participant when you perform the venipuncture.

8. If venipuncture becomes difficult, you may need to touch the vein again with your hand. If this happens, cleanse the site again with alcohol.

11.2.5.4 Perform Venipuncture

1. Explain the procedure to participant; for example, "I will be drawing a blood sample from your arm. You will probably feel a small prick when I insert the needle."
2. Grasp the participant's arm firmly, using your thumb to draw the skin taut. This anchors the vein. The thumb should be one or two inches (2.5 or 5.0 cm) below the venipuncture site.
3. Enter the vein in a smooth continuous motion with the needle bevel upward and parallel to the vein. Use a straight stab; do not poke around.
4. Make sure the participant's arm is in a flat and stable position.
5. Grasp the flange of the vacutainer holder and push the tube forward until the butt end of the needle punctures the stopper, exposing the full lumen of the needle.
6. Remove the tourniquet after blood is flowing into the tube. If no blood enters the tube, the needle may not be positioned in the vein. See *Section 11.2.6 - Blood Collection Problems* for possible action.
7. Keep a constant, slight forward pressure (in the direction of the needle) on the end of the tube. This prevents release of the shutoff valve from stopping blood flow. Do not vary pressure or reintroduce pressure after completion of the draw.
8. Draw each vacutainer tube in order (three royal blue, the 2 ml lavender for CBC, two light blue, and the 10 ml lavender). Fill each tube as completely as possible, that is, until the vacuum is exhausted and the blood flow stops. If a vacutainer tube fills only partially, remove the vacutainer tube and attach another without removing the needle from the vein.
9. When the blood flow ceases, remove the tube from the holder. The shutoff valve re-covers the point, stopping blood flow until you insert the next tube (if necessary).
10. Draw the required blood tubes and place the royal blue-stoppered tubes into sleeves of aluminum foil to protect from the light.
11. Gently invert the lavender and light blue-stopped vacutainer tubes several times to ensure proper mixing of blood with the anticoagulants before placing the tubes in the rack. Do not invert the royal blue-stoppered tube.
12. Label the form and each tube with a blood sample label immediately after you complete the blood draw. (You can best do this while the participant is holding the gauze pad over the venipuncture site; see the steps below.)

    For routine samples, put the first label (printed with "Form") from a blood sample label set on the front of *Form 100 - Blood Collection and Processing* in the space indicated for Blood Sample Number and a second label (also printed with "Form") on the back of the form.

11.2.5.5 Bandage the Arm

1. Under normal conditions:
   - To remove the needle, lightly place clean gauze over venipuncture site. Remove the needle quickly and immediately apply pressure to the site with a gauze pad. Discard needle with its cap into a needle box. If using a syringe with needle, dispose entire set-up into disposable container.
   - Have the participant hold the gauze pad firmly for one to two minutes to prevent a hematoma. Ask the participant to keep her arm extended. Bending her arm at the elbow increases the risk of developing a hematoma.
   - Apply an adhesive or gauze bandage over the venipuncture site after making sure that blood flow has stopped.

2. If the participant continues to bleed:
    - Apply pressure to the site with a gauze pad. Keep the arm elevated until the bleeding stops.
    - Wrap a gauze bandage tightly around the arm over the pad.
    - Tell the participant to leave the bandage on for at least 15 minutes.
3. Wash your hands.
4. Complete the remainder of the "Blood Collection" section of *Form 100 - Blood Collection and Processing*.
5. Deliver the blood sample tubes and *Form 100 - Blood Collection and Processing* to the blood processing area.

11.2.6 Blood Collection Problems

11.2.6.1 Special Consideration for Drawing Blood in the Elderly

The elderly pose some special blood drawing problems due to fragile and small veins, especially if the samples are drawn during a fasting period. The system of drawing blood by using vacuum tubes can increase this problem, causing veins to collapse due to high pressure exerted by the vacuum tubes. Steps outlined in *Section 11.2.6.3 - Difficult Venipuncture* below may help to lessen some of the problems.

An important point in drawing blood is that the tourniquet must not occlude arterial flow; otherwise the problem of veins collapsing during the venipuncture may be accentuated. By using a syringe rather than a vacuum tube, you can control the pressure and reduce this problem. When using a smaller needle (for example, 22 gauge 1"), there is less chance of blowing (hematoma formation) a fragile vein.

11.2.6.2 Difficult-to-Identify-Venipuncture Sites

1. Determine if the vein is difficult to identify, which may occur, if:
    - The palpitated vein feels small or rolls.
    - The participant has been stuck once already.
2. If the vein is difficult to find, check the back of the hand and forearm for venipuncture sites with larger veins. You can also try one or more of the following vein-dilation methods:
    - Be sure the room is not too cool.
    - Hot pack the venipuncture site with warm, wet towels for 3-5 minutes.
    - Have the participant wash her hands in warm water for 3-5 minutes.
    - Have the participant dangle her arm at her side with the tourniquet in place for one minute.
    - Use the blood pressure cuff as a tourniquet by pumping the pressure to 60-80 mm Hg.
3. If the vein is small, try a disposable syringe and 22-gauge needle or a butterfly initially.
4. Finish the venipuncture following the procedures outlined above.

11.2.6.3 Difficult Venipuncture

If you performed the venipuncture and a blood sample is not forthcoming, you may find the following manipulations helpful:

- If there is a sucking sound, turn the needle slightly or lift the holder to move the bevel away from the wall of the vein.

- If no blood appears, move the needle slightly in hopes of entering the vein. Do not probe. If unsuccessful, release the tourniquet and remove the needle. A second attempt can be made on the other arm.
- If the vein rolls, withdraw the needle slightly without coming back through the skin and try a second thrust.
- If the vein collapses, remove the vacutainer tube, call another staff person to reapply the tourniquet, ask the participant to open and close fist, and then reinsert tube. If still no blood appears in the tube, stop the procedure and use techniques in *Section 11.2.6.2 - Difficult-to-Identify-Venipuncture Sites* above.

  If this is a problem on a particular participant, try using a butterfly needle rather than a vacutainer needle to draw the blood.

  The participants come to the CC visit fasting for 12 hours (nothing but water) and may be dehydrated. Encourage the participants to drink water liberally during the fast. If this is a particular problem at your CC, consider offering the participants water as they arrive at the visit.
- Loosen the tourniquet. You may have applied it too tightly, thereby stopping the blood flow. Reapply the tourniquet loosely. If the tourniquet is a Velcro type, quickly release and press back together. Be sure, however, that the tourniquet remains on for no longer than one minute at a time.
- Remove the tube and insert a second vacutainer tube. On rare occasions, the vacutainer tube may have lost its vacuum and thus may not draw blood into the tube even when the needle is positioned properly in the vein.
- If another technician is available, allow the other technician to attempt a venipuncture.
- If venipuncture fails with the second technician, request that the participant return at another time for a successful venipuncture. (See *Section 11.2.6.5 - Deficient Serum and Plasma Sample*.)
- Reassure the participant that the inability to obtain a clean venipuncture is not any sign of a medical problem on her part.
- No single staff member should attempt more than two venipunctures on the same participant at any single visit. See *Section 11.2.4.4 - Preparation at the Visit* for instructions on specific tubes to draw at the second blood draw occasion.

11.2.6.4 Fainting

If participant shows signs of fainting (loss of color in the face, unusual sweating on forehead) or reports feeling dizzy:

- Finish drawing blood if possible but do not proceed if participant is clearly in trouble.
- Have participant lay her head on a table.
- Continue talking to participant to assess level of consciousness.
- Have participant lie down for 5-10 minutes after removing the needle; apply pressure on vein to prevent injuries from possible fall or seizure.
- Apply cool compress to her forehead.
- Have participant put a pillow or cushion under her knees.

If the participant faints:

- Withdraw the needle immediately.
- Apply pressure at the venipuncture site.
- Call for help.

- Apply a cool compress to her forehead.
- Use an ammonia capsule, if needed, by crushing the ampule and waving it under her nose for a few seconds.
- Once recovered, have the participant lie down on an exam table until she feels better.
- Take blood pressure readings to assess her recovery, if necessary.
- Offer the participant water, juice and food.

Note: If you do not collect a blood sample, reschedule the blood draw for another day.

Realize that the participant might be disoriented, embarrassed, or irritable and needs reassurance and attention. Recognize also that this incident may have an impact on future blood drawing and possibly on study adherence and must be handled well. Make a note of the difficulty in the participant's file for future reference.

11.2.6.5 Deficient Serum and Plasma Samples

Common reasons for failure to obtain enough specimen include:

- Original vacutainers not properly filled.
- Adequate time not allowed for clot formation (royal blue-stoppered tubes only).
- Failure of centrifuge to attain required relative centrifugal force. Check or ask service representative to check the relative centrifugal force (RCF) every six months or when you begin to experience more frequent insufficient sample problems.
- High hematocrit of participant. This can be more common in people with asthma or emphysema. Note this in the participant's file and draw more tubes of blood at subsequent blood draws so these participants do not have deficient samples each time.
- Over-filling the sample cryovials.

If you do not get a full royal blue-stoppered vacutainer of blood (for serum), you should try to collect an additional half-tube immediately. After centrifuging the tubes, you can combine the serum from the half-tube with the serum from the first incompletely filled royal blue-stoppered tubes. Similarly, if you do not get full light-blue or lavender tubes, you should try to collect additional tubes. However, you must fill these tubes as full as possible to get the proper proportion of blood to anticoagulant.

If you do not obtain sufficient blood in the first attempt, perform a second venipuncture (see *Section 11.2.6.3 – Difficult Venipuncture*).

Deficient Samples

There may be an occasion where the blood draw may yield less than you need to fill all the tubes. In general, blood collected from different blood draws within a short time (e.g., less than one hour) can be considered the same blood draw. Blood collected on different days or different times (> 1 hour apart) are considered different draws and require two separate *Form 100*s with different blood sample numbers. To do a second blood draw, complete a new *Form 100 - Blood Collection and Processing*, assign a new blood sample number, and answer the questions on the form as you would for any blood draw.

- **At SV1:**

  For CT participants, if you do not collect enough blood samples for the triglycerides [if serum is lipemic for HRT participants] or CBC at SV1, collect additional blood for the triglycerides or CBC at SV2. At SV2 it is essential to collect sufficient samples for the local lab analysis of hematocrit and platelet count and for triglycerides (if an HRT participant's serum is lipemic) because you cannot randomize a

participant at Screening Visit 3 (SV3) without these results. It is not necessary to obtain the rest of a deficient screening sample after the participant is randomized. It is better to try to get the rest of the sample before randomization if the additional attempt would not adversely effect the participant's willingness to join the study.

For OS participants, you must obtain at least 2 ml of serum for a participant to be eligible for enrollment into OS. This means that a minimum draw of 4 ml of blood in a royal blue tube is necessary (to make 2 ml of serum). Thus, at least 2 aliquots should be sent to McKesson BioServices (1 ml each in cryovial -02 and -03; fill the cryovial to the 1.8 ml mark only if you have enough blood for 1 ml in all required aliquots). For OS, collection of the local lab has a lower priority, and attempts should be made to collect the blood for McKesson BioServices before collecting the CBC blood.

- **At Annual Visits:**

  You do not need to make additional contacts or visits to collect missing blood samples.

11.2.7 Summary of Blood Collection Procedure

1. Label *Form 100 - Blood Collection and Processing* with the participant's name and ID number.
2. Obtain a set of blood sample labels and attach to *Form 100 - Blood Collection and Processing.*
3. Review the blood collection aliquot schedule portion of *Form 100 - Blood Collection and Processing* indicating the type of blood you need to collect.

At the Visit:

1. Check that *Form 100 - Blood Collection and Processing* is correctly labeled with the participant's name and ID number.
2. Review the section of the form indicating the number of tubes to draw.
3. Instruct the participant.
4. Collect the blood.
5. Apply a blood sample label to *Form 100 - Blood Collection and Processing* in the spaces indicated.
6. Label the blood collection tubes with the blood sample labels.
7. Cover the royal blue-stoppered tubes with foil.
8. Gently invert light blue and lavender tubes several times after each tube is drawn.
9. Complete the remainder of the Blood Collection section of *Form 100 - Blood Collection and Processing*. Ensure first page is completed.
10. Deliver the blood sample tubes and *Form 100 - Blood Collection and Processing* to the blood processing area.

11.3 Blood Processing

11.3.1 Timelimits and Sample Handling

Procedures and time limits for blood processing are listed below. See also *Figure 11.3 - Guidelines for Blood Processing.*

1. Stand time:
   - Allow the royal blue-stoppered tubes to stand for at least 30 minutes at room temperature. The 30-minute waiting time is necessary to allow an adequate clot to form. If you frequently find fibrin clots in the centrifuged serum samples, try letting the samples sit for 45 minutes before centrifugation.
     - Always protect blood samples for carotenoids (in royal blue-stoppered tubes) from natural and fluorescent white light. Store samples in covered containers or tubes.
2. Refrigerate time:
   - Refrigerate the royal blue (after clotting), light blue and 10 ml lavender tubes if it is not possible to centrifuge the samples within one hour after collection.
   - Set the samples in wet ice if a refrigerator is not available.
3. Centrifuge time:
   - Make every attempt to centrifuge the tubes between 30-45 minutes after collection. Set a timer, if necessary, as a reminder when the collected blood is ready for centrifugation.
   - Centrifuge the royal blue and light blue tubes within two hours of collection.
   - Centrifuge the 10 ml lavender tube within four hours of collection.
4. Aliquot time:
   - Aliquot the serum and plasma into the cryovials within 15 minutes after centrifugation.
5. Freeze time:
   - Freeze all aliquoted specimens within two hours of collection.

11.3.1.1 CBC

Do not refrigerate the tube for the CBC unless it is requested by your local lab. Send the 2 ml lavender stoppered tube to your local lab for a CBC analysis and a platelet count. Do not centrifuge the tube for the CBC. Follow your local CC procedures for completing the paperwork.

Figure 11.3
Guidelines for Blood Processing

Blood Collection Tube	Minimum Stand Time at Room Temp.	Maximum Stand Time at Room Temp. (before refrigeration)	Min. Time Post-blood Collection to Begin Centrifugation	Max. Time to Begin Centrifugation	Centrifuge Time	Post-Centrifugation Aliquot Time	Freeze Time Post Collection
Royal blue (7 ml)	30 min.	1 hr	≥ 30 min	2 hours post collection	10 minutes	15 minutes post-centrifugation	Within 2 hours post collection
Light blue (4.5 ml)	0 min	1 hr	Immediately post-collection	2 hours post collection	10 minutes	15 minutes post-centrifugation	Within 2 hours post-collection
Lavender (10 ml)	0 min	1 hr	Immediately post-collection	4 hours post-collection	10 minutes	15 minutes post centrifugation	Within 2 hours post-collection
Lavender (2 ml)	0 min	n/a	n/a	n/a	n/a	n/a	n/a

11.3.2 Operating the Refrigerated Centrifuge

1. Set the centrifuge temperature at 4°C. (A setting in the 2° to 8°C range is acceptable.)
2. Load the rotor, being careful to place balanced tubes in buckets directly opposite to each other. If necessary, fill an empty tube with water, insert stopper and use as a balance for a blood sample tube. Be sure there is enough clearance for the tube and stopper when the buckets are in horizontal position.
3. Close the centrifuge cover and lock.
4. Centrifuge for ten minutes with brake off at a speed setting that will yield a relative centrifugal force (RCF) of 1,300 xg.

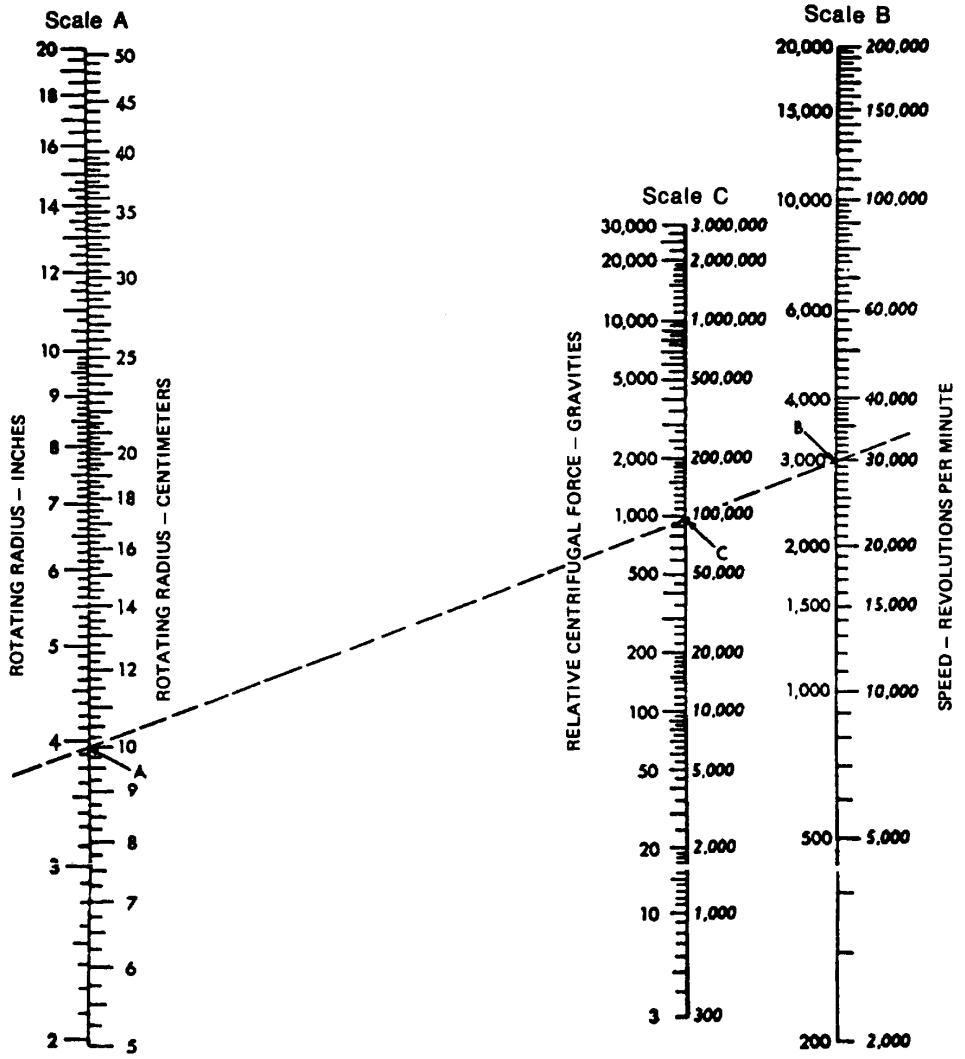
   You can obtain the desired RCF of 1,300 xg on various centrifuges by adjusting the revolutions per minute (RPM). You need to do this because the RPM setting of a centrifuge does not equal the RCF. The following equation shows the calculation of RCF:

   $$RCF = (1.118)(10^{-5})(r)(n^2)$$

   where r = rotating radius in centimeters (the distance from the center of the centrifuge rotor to the middle of the sample tube when the tubes in the swinging buckets are at the horizontal position) and n = revolutions per minute.

   Alternately, use *Figure 11.4 - Nomogram for Calculating RCF* by lining up the radius in cm and RCF = 1,300 xg with a straight edge and reading the point at which the straight edge intersects the scale for RPM. For example, to achieve RCF of 1,300 xg with a centrifuge that has a radius of 10 cm, a straight line from these points on *Figure 11.4 - Nomogram for Calculating RCF* intersects the RPM scale at 3,400 RPM.
5. Record the time you started the centrifuge on *Form 100 - Blood Collection and Processing*. Do not use the time when you removed the samples from the centrifuge.
6. The centrifuge will stop automatically at the prescribed time. Allow the centrifuge to come to a complete stop before opening the cover. Do not use the brake to slow down the centrifuge. Using the brake may cause the RBCs to become resuspended in the plasma.
7. Remove the blood sample tubes one at a time and put in the test tube rack. Be careful not to tip the tubes and disturb the red cell layer. Re-centrifuge any tube containing red blood cells in the serum or plasma.
8. Consult the Centrifuge Service manual for other guidelines and for troubleshooting.

Figure 11.4
Nomogram for Calculating RCF



*Modified from the IEC (a division of Damon Corporation, Needham Heights, Mass.) Relative Centrifugal Force Nomograph.

11.3.3 Processing Samples

You can process several blood samples at a time as long as you follow the timing guidelines listed in *Section 11.3.1 - Timelimits and Handling* above and in *Figure 11.3 - Guidelines for Blood Processing.* To keep the blood samples you are processing separate, keep the blood collection and cryovials from each participant in a separate rack. This will help you aliquot the samples into the correct corresponding cryovials.

The following is an example of how you can set up your work area and process several blood samples at one time. You may change the procedure as needed to make the processing more efficient at your CC.

- Set up a separate rack for each participant's set of blood samples. Because the cryovials fit better in a rack with smaller holes, you can use two racks for each blood sample: the one with smaller holes for the cryovials in front, and one with larger holes for the blood collection tubes directly behind the smaller rack. See *Figure 11.5 - Sample Blood Processing Rack Set-Up* below for an example set-up of tubes.
- When you first get the blood sample tubes, put the protected royal blue tubes in the appropriate racks to stand for 30 minutes and allow the blood to clot. Keep the tubes protected from light during this waiting time.
- Centrifuge the light blue and 10 ml lavender tubes for ten minutes.
- While the samples are centrifuging, label the cryovials. Place the labeled cryovials in the smaller rack. Remove the caps and lay them in front of the corresponding cryovials in the rack.
- When you have time, process the 2 ml lavender tube by completing the local lab paperwork for the CBC and platelet count as needed.
- When the centrifuge stops, place the tubes from the centrifuge in the appropriate larger racks, placing the tubes directly behind the row of cryovials into which you will be placing the plasma.
- Process the plasma from the light blue and lavender tubes as described in *Section 11.3.3.1 - Preparation of Blood Cryovials* below. Process only one set of colored tubes from one blood sample at a time (e.g., process plasma from the light blue tubes before processing plasma from the lavender tubes). This will help reduce the chance of mixing serum and different types of plasma from one participant and from mixing samples between different participants.
- After processing the plasma from the 10 ml lavender tube, process the buffy coat and RBCs as described in *Section 11.3.3.1 - Preparation of Blood Cryovials* .
- When 30 minutes have passed, centrifuge the royal blue tubes. While the tubes are centrifuging, you can complete processing of the light blue and lavender tubes and the 2 ml lavender tube for the CBC, if you have not already done so.
- Follow the procedure in *Section 11.3.3.1 - Preparation of Blood Cryovials* for processing the serum from the royal blue tube.
- Place the samples in the freezer box. Complete the Blood Processing portion of *Form 100 - Blood Collection and Processing* as you place the aliquots into the freezer box, marking the corresponding aliquot on the form, as you place the aliquot into the freezer box.

Figure 11.5
Sample Blood Processing Rack Set-Up

Rack for Blood Collection Tubes

									Back
Royal Blue									
Royal Blue		Light Blue							
Royal Blue		Light Blue		10 ml Lavender					**Front**

Rack for Blood Cryovials

-09		-20		-14					**Back**
-05				-13					
-04		-08		-12					
-03		-07		-11					
-02		-06		-10					**Front**

11.3.3.1 Preparation of Blood Cryovials (Required)

1. Place the 2 ml lavender-stoppered tube and the centrifuged tubes from each participant in separate racks.
2. Inspect each centrifuged tube for hemolysis. Recentrifuge any specimen that contains red cells suspended in the serum or plasma. If a specimen is badly hemolyzed, do not use the specimen for preparing aliquots for storage.
3. For HRT or HRT+DM participants, determine if you need to process an aliquot sample for triglycerides.
   - Inspect the royal blue-stoppered tube for lipemia (serum will appear opaque or milky). Use the laminated "Test Print" card and the photograph of tubes of varying triglyceride levels supplied by MRL.
     – In the photograph, the tube on the left, labeled "Normal Trig.", contains clear serum, indicating that the triglyceride is not elevated above 300 mg/dl. The print behind the tube is clearly seem through the serum.

  - The middle tube, labeled "Trig. 300," contains serum that appears slightly turbid. Though the print behind the tube can still be seen, the print is distorted and not easily read. This tube represents a triglyceride of 300 mg/dl.
  - The tube on the right, labeled "Trig. 500," contains serum with triglyceride of 500 ml/dl. This serum is turbid and you cannot read the print through the tube.

- Hold the participant's royal blue-stoppered tube up to the laminated "Test Print" card and compare the visibility of the print with the tubes in the photograph.
- If the participant's serum appears as turbid as the tube labeled "Trig. 500", the serum is considered lipemic. Prepare a 0.5 ml serum aliquot as directed under step 6 below and send to your CC's local lab for a triglyceride level. Use local CC procedures to complete the paperwork.

4. Review the Blood Request information on *Form 100 - Blood Collection and Processing* to determine the number of cryovials to prepare.

5. Using the 13 blood sample labels for the cryovials, label each cryovial you will need. For the triglyceride level you can use vials supplied by McKesson BioServices, purchased by your CC, or supplied by the local lab. (*Note:* Each cryovial is marked with a line indicating the 1.8 ml mark. Because you should not fill the cryovials over this line, try not to cover the 1.8 ml mark with the label. Wrap the label around the cryovial, placing one side on the bottom edge of the cryovial as shown below.) Refer to *Figure 11.6 - Processing Blood Samples* for a guide for labeling cryovials.

6. **When you remove the stoppers from the blood collection tubes that do not have hemoguards, remove them behind a work shield or wear a face shield to avoid potential exposure to aerosol.** Transfer the serum and plasma to the cryovials as described below. For each blood sample, use a different clean pipette tip for each specimen type (i.e., use one for the serum in the royal blue tube, a different one for the plasma in the light blue tubes, and a different one for plasma in the lavender tubes.)

   At the time of the transfer, check to make sure that you place the correct specimen in the correct cryovial. When you fill the cryovials, do not fill the cryovial over the 1.8 ml mark on the vial. You must leave a small pocket of air at the top of the vial to prevent breakage during freezing.

   - Remove the stopper from the light blue-stoppered tube.

     Transfer 1.8 ml of plasma to each of three cryovials (numbered -06 to -08). If you are not certain that you have sufficient plasma to fill each of the three cryovials with 1.8 ml plasma, first fill each vial with 1.0 ml plasma then add an additional 0.8 ml plasma to each vial. Screw the lids onto the three cryovials.

     Remove the buffy coat layer from both light blue tubes and place in cryovial labeled "Buffy Coat" numbered -20. To process the buffy coat, remove the buffy coat along with approximately 1.5 to 1.8 ml of the RBCs. (Including the RBCs with the buffy coat will help ensure better recovery of the WBCs used in the DNA extractions.) Screw the lid onto the cryovial.

     Insert the light blue stoppers back in the blood collection tubes and place the tubes and pipette tip in a biohazard container.

   - Remove the stopper from the 10 ml lavender-stoppered tube.

     Transfer the plasma to the three cryovials (numbered -10 to -12). Put 1.8 ml plasma in the vials numbered -10, -11, and -12. If you are not certain that you have sufficient plasma to fill each of the three cryovials with 1.8 ml plasma, first fill each vial with 1.0 ml plasma then add an additional 0.8 ml plasma to each vial. Screw the lids onto the three cryovials, the buffy coat and RBC aliquots as follows:

     1. Remove the buffy coat layer and place in the cryovial (labeled "Buffy Coat" and numbered -13.) To process the buffy coat, remove the buffy coat along with approximately 1.5 to 1.8 ml of the RBCs. (Including the RBCs with the buffy coat will help ensure better recovery of the WBCs used in the DNA extractions.) Leave sufficient RBCs in the tube to process for RBC only aliquot (-14). Screw the lid onto the cryovial.

2. Aliquot 1.8 ml of the packed RBCs into one cryovial (labeled "RBC" and numbered -14). Screw the lid on the vial.

- Remove the stopper from the royal blue-stoppered tube.

  If you need a triglyceride level (as described above for HRT and HRT+DM participants), transfer 0.5 ml of serum to the local lab's cryovial (labeled "Triglyceride" and numbered -09).

  Transfer 1.8 ml of serum to each of four vials (numbered -02 to -05). If you are not certain that you have sufficient serum to fill each of the four cryovials with 1.8 ml serum, first fill each of the vials with 1.0 ml serum. Then add an additional 0.8 ml serum to each vial. This will help assure that you get sample in each of the four cryovials. Screw the lids onto the four cryovials. Place the four vials in a box and cover with a lid to protect the serum from white light. Insert the royal blue stoppers back into the blood collection tubes. Place the blood collection tube and the pipette tip in a biohazard container.

7. Check all cryovials to be sure you have correctly labeled them.

8. Label the 2 ml lavender blood collection tube with the cryovial labeled "CBC" and numbered -16. Follow CC procedures for sending the specimen to the local lab.

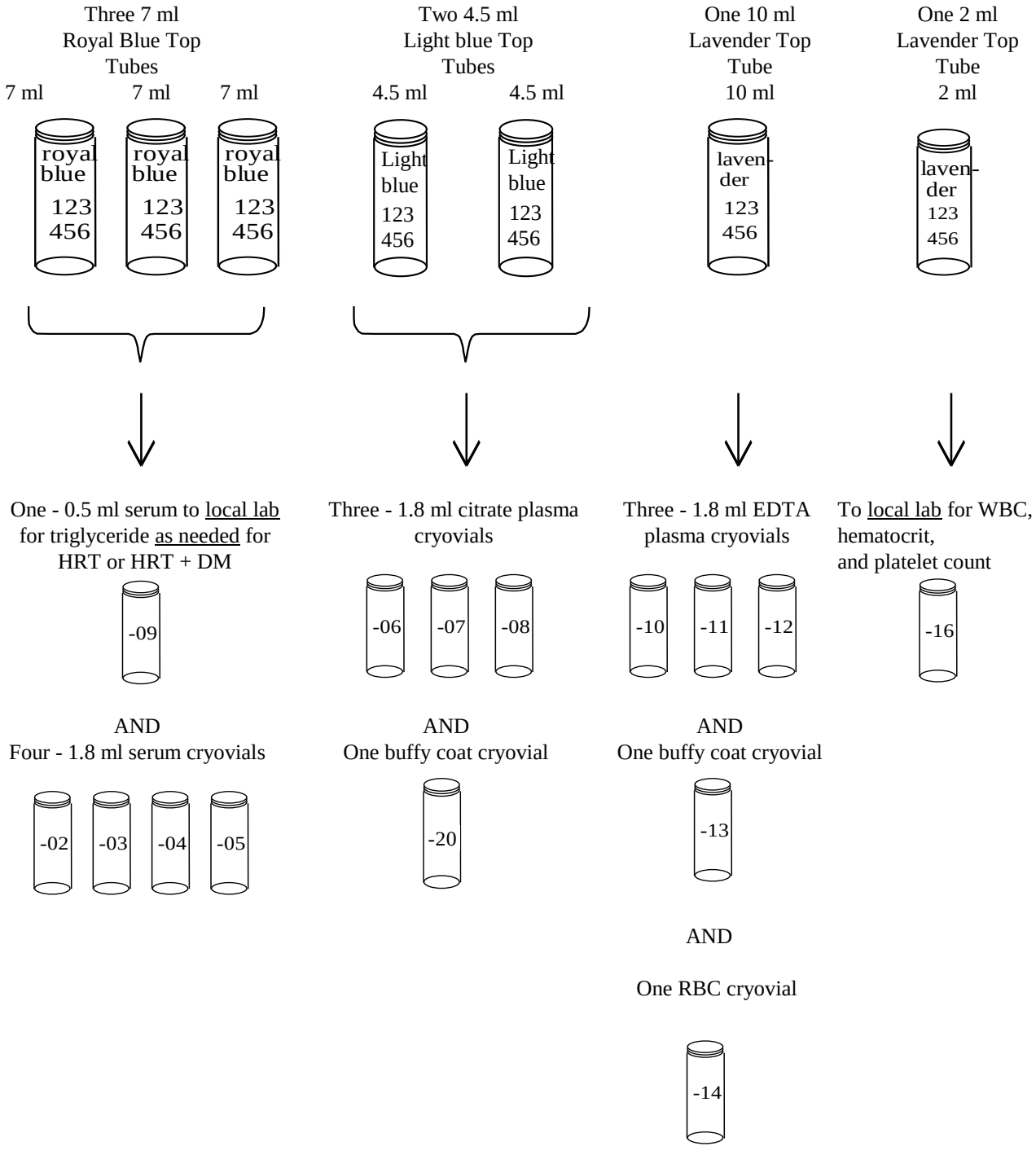
9. Complete the Blood Processing portion of *Form 100 - Blood Collection and Processing*.

   Record the centrifuge time and time placed in the freezer for the lavender tube and corresponding cryovials.

   Mark the box corresponding to each cryovial you processed to indicate you prepared the cryovial and the CBC collection tube. If you did not process a particular cryovial or process a tube for the CBC, do not mark the corresponding box. Double check each cryovial marked on *Form 100 - Blood Collection and Processing*, as you place each cryovial in the freezer box.

Figure 11.6
Processing Blood Samples

(Example for blood sample #123456)



11.3.4 Tracking Specimens for Local Lab

Follow your CC procedures for tracking CBC and triglyceride specimens, and receiving the corresponding results. Examples of activities to include in the procedures include:

- Which specimens you sent to the local lab, the date sent, and the tests ordered.
- Handling results as they return, including how to pair the results with the corresponding *Form 100 - Blood Collection and Processing.*
- Review of the results, including review for eligibility and abnormalities and handling of abnormalities that require follow-up.
- Processing the paperwork, including key-entry of the *Form 100 - Blood Collection and Processing* and the results, and filing both in the participant's file.

11.3.5 Freezing and Storing Blood Cryovials (Required)

Store the processed cryovials in labeled freezer storage boxes as described below.

1. Assign a sequential frozen shipment number to each frozen shipment you send to McKesson BioServices, starting with number "1". Do not use duplicate numbers for two batches since McKesson BioServices cannot track duplicate batch numbers. Do not skip numbers, since the skipped numbers indicate a missing or lost batch. **[Optional]**
2. Label any side of both the freezer storage box and lid with your CC number, frozen shipment number, and a box sequence number. The side you label becomes the front of the box. Start the box sequence number with "1" for each month's shipment. For example, use "43-011-2" for the CC with an ID number of 43, frozen shipment number 11, and box number 2. (Labeling the sides of the freezer boxes sent to McKesson BioServices is optional and is no longer required.) **[Optional]**
3. Insert the storage box divider into the box.
4. Place the frozen cryovials in the freezer storage box. You can put the cryovials in any order in the box. For this description, the positions in the storage box are numbered from 1 to 81, starting with the front left, and running from left to right in rows from front to back. See *Figure 11.7 - Specimen Storage Box.* Starting with position number 1 and continuing to fill the box in sequence until the box is full can help you locate a sample if necessary. If all the cryovials will not fit in one box, fill the current box and then begin filling the next storage box. You can put cryovials from different participants in the same box and samples from one participant in two separate boxes.
5. Place the box in the -70°C freezer. Samples must be frozen at least <u>two hours</u> before packing them for shipment to McKesson BioServices. If you do not have a -70°C freezer available, put the cryovials in a -20°C freezer immediately after aliquoting. Then transfer to a -70°C freezer as soon as possible but no longer than two days (over the weekend). Placing the samples on wet ice or dry ice does not sufficiently preserve the sample, so you must put the samples in at least a -20°C freezer. <u>Do not thaw the samples after freezing</u>. If frozen samples are thawed (i.e., the result of a freezer failure) contact the CCC for instructions.

   If after freezing, you find a cryovial is broken, do not send it to McKesson BioServices. Place it in the biohazard container. Record the information of the breakage on a log sheet and edit the corresponding *Form 100 - Blood Collection and Processing* to indicate that you are not sending the broken sample to McKesson. A broken cryovial may indicate more than 1.8 ml of serum was added to the cryovial. Review the blood processing procedures to ensure blood processing staff do not overfill the vials.

11.3.5.1 Equipment Quality Assurance (Required)

- **Centrifuge**

  Monitor the temperature of the refrigerated centrifuge daily using the temperature gauge on the centrifuge. Measure the temperature before centrifugation. Recording each temperature check on a log sheet is optional.

  Once each month, check the temperature of the centrifuge using a certified temperature thermometer in the 0°C to 10°C range. Do this even if you have an internal digital thermometer, as this will then also check the accuracy of the digital thermometer. You may do this by laying the thermometer on the bottom of the centrifuge.

  Once each year, check the speed of the centrifuge using a tachometer. Perform routine maintenance as suggested by the centrifuge manufacturer. A centrifuge maintenance log can be used to record these routine equipment checks and maintenance at the CC's discretion and is optional.

- **Freezer**

  Monitor the temperature of the freezer daily using a certified low temperature thermometer in the -70°C range or a digit temperature display that may be on the freezer. If you use the digit display for the daily temperature checks, check the temperature of the freezer using a certified thermometer in the -80°C to -60°C range at least once each month. Recording each temperature check on a log sheet is optional.

  Each month check the CO_2 tank to be sure it has not been emptied. Also test the alarm system to be sure it will sound should the freezer temperature rise above -50°C. As of January 1997, CCs are required to have an alarm system attached to each -70°C freezer. An appropriate system must have the capacity to monitor the freezer and to call multiple phone numbers should malfunction occur. See *Section 2.3.2.5 - Blood and Urine Collection, Processing, and Shipment* for recommended alarm system.

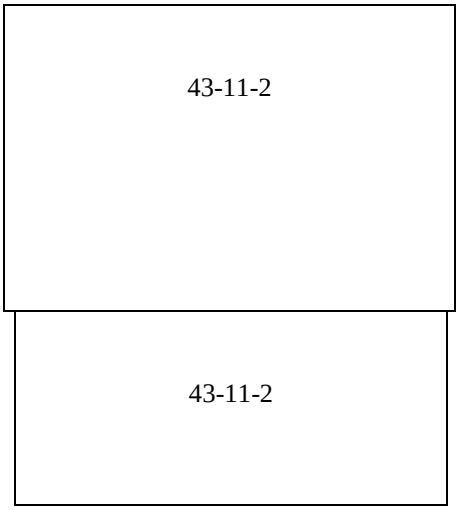
  Perform routine maintenance as suggested by the freezer manufacturer such as routine freezer defrosting and record in freezer maintenance log. Make sure there are no samples in the freezer when you defrost it. You can coordinate the timing of the defrosting with the shipment of samples to McKesson BioServices; or use temporary storage in another freezer during the defrosting.

11.3.6 Summary of Blood Processing Procedures

1. Send blood sample aliquots to the local lab for WBC, hematocrit and platelet count and for triglyceride as needed (for HRT and HRT+DM participants with lipemic serum).
2. Allow royal blue tubes to sit at least 30 minutes before centrifuging. Refrigerate them and any other tubes if you cannot centrifuge within one hour. Centrifuge the royal blue tube and light blue tubes within two hours of collection. Centrifuge the 10 ml lavender tube within four hours of collection. Freeze all samples within two hours of collection.
3. Set up and label cryovials corresponding to the aliquots to be prepared.
4. Transfer serum and plasma into appropriate cryovials within 15 minutes post centrifugation.
5. Cap the vials securely.
6. Prepare the RBC and buffy coat aliquots.
7. Place cryovials in the freezer boxes and place in freezer, checking each cryovial number with the cryovials marked on *Form 100 - Blood Collection and Processing.*

Figure 11.7
Specimen Storage Box

Front view of box and lid



← Lid

Example: 43 - Clinical Center ID#
11 - Frozen shipment number
2 - Box 2 of this shipment

← Bottom

Top View of Box

73								81
64								72
55								63
46								54
37								45
28								36
19								27
10								18
1	2	3	4	5	6	7	8	9

Front

Numbers indicate position numbers inside of storage box

11.4 Blood Storage and Shipping

11.4.1 Shipping Schedule (Required)

Ship frozen serum samples to McKesson BioServices at least once every three months. Make shipments by mid- February, May, August, and November to ensure McKesson has sufficient time to log in the blood samples before the database consolidation at the end of the month. A quarterly shipping of blood specimens by the CC is required. CCs may make more frequent shiipments at the CC's discretion. All CCs must ensure that frozen samples are shipped on a quarterly basis to McKesson BioServices regardless of the number of samples in the freezer.

Ship on a Monday, Tuesday or Wednesday. Do not ship on a day before a McKesson BioServices holiday. McKesson BioServices holidays are: New Year's Day, President's Day, Memorial Day, Independence Day, Labor Day, Columbus Day, Veteran's Day, Thanksgiving, and Christmas.

Samples must be frozen at least two hours at -70°C before packing them for shipment. If the blood samples were drawn on the same day you plan to ship them to McKesson, to help with freezing, leave the lid off the freezer box until it is ready to be packed for shipment. If the insulated shipping container is not filled, stuff newspapers to stabilize the freezer boxes.

11.4.1.1 Mailing Instructions (Required)

Ship the fiberboard shipping box with frozen samples to McKesson BioServices by day or overnight courier to ensure receipt at McKesson BioServices within 24 hours.

There is no minimum number of cryovials to include in a shipment; ship all frozen cryovials regardless of the number of specimens that have been frozen and stored within the last collection period. However, CCs must follow current International Air Transport Association (IATA) regulations. As of January 1997, IATA Dangerous Goods Regulations have changed. The maximum allowable volume of diagnostic specimens allowed in a shipping container has increased from 500 ml to 4 liters (4000 ml). You can send up to 16 freezer boxes in the large shipping container. Include all the blood aliquots you have drawn and frozen.

Form 104 - Frozen Specimen Shipment has been replaced with the McKesson BioServices form Notification of WHI Shipment. CCs use this form to record shipping information and to order blood collection and shipping supplies. The CC is responsible for faxing the Notification of WHI Shipment form (Figure 11.7A) to McKesson when the CC sends a blood shipment. Upon receiving the blood shipment, McKesson will complete the "Confirmation of Receipt" section of the Notification of WHI Shipment form and send it to the CC. If the required WHI Notification of Shipment form is not sent to McKesson by the CC, then McKesson cannot return a Confirmation of Receipt.

11.4.1.2 Mailing Instructions for Visiting Participants (Required)

Two options may be used for ensuring blood samples are sent to McKesson when a participant has her blood drawn while she is visiting another CC:

- One option is to perform the blood draw and processing at the visiting CC and return the completed *Form 100 – Blood Collection and Processing* and frozen blood samples to the permanent CC.
- The second option is to perform the blood draw and processing at the visiting CC, return the completed *Form 100 – Blood Collection and Processing* to the permanent CC and ship the frozen blood samples directly to McKesson.

The option that you select to use should be a mutually agreeable process by both the "permanent CC" and the "visiting CC." Note that the work scope for the permanent CC is the same for both options. The work scope for the visiting CC is dependent on the option choice.

Figure 11.7A
Notification of WHI Shipment

NOTIFICATION OF WHI SHIPMENT

FAX TO (301) 838-9753

CENTER INFORMATION:

_____
Center

_____
Name

_____
Phone Number

_____
Fax Number

SHIPPING INFORMATION:

Number of Shipping Boxes: _____

Number of Freezer Boxes: _____

Shipment date: _____

Airbill Numbers: _____

_____ _____

_____ _____

_____ _____

CONFIRMATION OF RECIEPT

Date of Receipt: _____

Number of Boxes Received: _____

Samples were received:

_____ Frozen

_____ Thawed

COMMENTS: _____

_____

SEND THE FOLLOWING SUPPLIES:

BLOOD COLLECTION SUPPLIES

Serum Tubes (Royal Blue) 7ml
No additives – for trace elements
100 tubes/pk _____pk
10 tubes/pk _____pk

Plasma Tubes (Lavender) 10ml
Power additive – EDTA (Na2)
100 tubes/pk _____pk
10 tubes/pk _____pk

Plasma Tubes (Light Blue) 4.5ml
3.8% Buffered Citrate Solution
100 tubes/pk _____pk
10 tubes/pk _____pk

STORAGE SUPPLIES

Cryovials: 100 vials/bag _____bag

Freezer Storage boxes _____boxes
includes 81 cell divider

LABLES

Barcode Labels (Blood) _____sets
Shipped in groups of 100

Barcodes Labels (Urine) _____sets
Shipping in sets of 100

SHIPPING SUPPLIES

Ziplock Bags _____groups
Shipped in groups of 5

Vial Shipping Boxes (Lg) _____boxes
Holds 8-12 freezer storage boxes

Vial Shipping boxes (Sm) _____boxes
Holds 1-5 freezer storage boxes

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Option One

The permanent CC has responsibility for the following:

- Complete as much of the visit as possible by phone and/or mail.
- Create a new employee ID in WHILMA and give it the employee name "other CC."
- Apply a participant ID label, complete the employee ID ("other CC"), visit type and visit year. Clip a set of blood labels to the *Form 100 – Blood Collection and Processing*.
- Send the *Form 100 – Blood Collection and Processing* to the visiting CC that will perform the blood draw along with a self-addressed envelope to facilitate the form's return.

The visiting CC has responsibility for the following:

- Perform the blood draw. Record the name of the staff person drawing the blood alongside the "drawn by" box.
- Process and freeze the blood samples. Record the name of the staff person processing the blood alongside the "processed by" box.
- Return the completed Form 100 – Blood Collection and Processing, including CBC results, applicable for the OS AV3, to the permanent CC in the self-addressed envelope (or enclose it in an airtight plastic bag in the shipping container along with the blood samples).
- Ship the frozen blood samples to the permanent CC to ship to McKesson.
- Phone, FAX or email the permanent CC to advise of the shipment.

Option Two

The permanent CC has responsibility for the following:

- Complete as much of the visit as possible by phone and/or mail.
- Create a new employee ID in WHILMA and give it the employee name "other CC."
- Apply a participant ID label, complete the employee ID ("other CC"), visit type and visit year. Clip a set of blood labels to the *Form 100 – Blood Collection and Processing*.
- Send the *Form 100 – Blood Collection and Processing* to the visiting CC that will perform the blood draw along with a self-addressed envelope to facilitate the form's return.

The visiting CC has responsibility for the following:

- Perform the blood draw. Record the name of the staff person drawing the blood alongside the "drawn by" box.
- Process and freeze the blood samples. Record the name of the staff person processing the blood alongside the "processed by" box.
- Return the completed *Form 100 – Blood Collection and Processing*, including CBC results, applicable for the OS AV3, to the permanent CC in the self-addressed envelope.
- Email McKesson to notify them that additional blood samples from another CC will be included in the routine monthly shipment of blood. Include the permanent CC's two digit ID number in the email.
- Place a note on the top of the styrofoam cover, on the insulating portion of the shipping box, indicating that the shipment contains blood samples from another CC.
- Place a note on the top of the freezer box indicating that blood samples from another CC are included in the freezer box.
- Ship the blood samples to McKesson with the routine monthly shipment.

11.4.2 Packaging Instructions (Required)

Pack the freezer storage boxes of frozen blood and urine samples in the shipping boxes as follows:

(The shipping box is composed of an inner styrofoam insulating portion and an outer fiberboard shell).

1. On the day of shipment, complete the Notification of WHI Shipment form to provide shipment information and/or to request supplies from McKesson. FAX the form to McKesson at 301-838-9753 and retain a copy for your records.

2. Wrap the freezer storage boxes containing the WHI samples in absorbent material (paper towels, wadding, etc.).

3. Place the freezer storage boxes in a plastic bag, either self-sealed zip-lock bag or secured with a waterproof seal. Remove as much of the air from the bag as possible and seal.

4. If you are using the smaller shipping box, place a minimum of 5-8 1bs of dry ice nuggets on the bottom. Place a maximum of 5 freezer storage boxes on top of the dry ice layer and then scatter the remaining 5-8 lbs. of dry ice nuggets around the freezer storage boxes. A minimum of 10 lbs. of dry ice and a maximum of 16 lbs. of dry ice can be used for the small shipping box. This will allow the package to remain frozen for 48 hours in case the shipment is delayed.

5. If you are using the larger shipping box, place a 8-10 lbs. of dry ice nuggets on the bottom. Place a maximum of 16 boxes on top of the dry ice layer and then scatter the remaining 8-10 lbs. of dry ice nuggets around the freezer storage boxes. A minimum of 16 lbs. of dry ice and a maximum of 20 lbs. of dry ice can be used for the large shipping box. This will allow the package to remain frozen for 48 hours in case shipment is delayed.

6. Stuff any empty space in the shipping box with newspaper or absorbent material.

7. Place the styrofoam cover on the insulating portion of the shipping box with the Notification of Shipment Form taped to the top. DO NOT TAPE the styrofoam cover to allow the dry ice gas to escape. Close and tape the outer fiberboard shell of the shipping box by sealing the top and corners of the box with waterproof tape to keep as much cool air as possible from escaping. Do not use scotch or masking tape.

8. Attach the airbill holder to the front of the box. Place the following labels on the top of the shipping box, so that none of the labels touch each other.

Label	Location on Fiberboard Box
Clinical Center's return address label	Top, upper left corner
McKesson BioServices address label	Top, lower right corner
Black-and-white class "9" label	Top, under Return address
Priority overnight label (optional)	Top, upper right corner
Diagnostic specimen label	Anywhere on top
Keep Frozen label (optional)	Anywhere on top

See Figure 11.8 - Frozen Specimen Shipping Labels to see sample labels and placement of the labels on top of the fiberboard shipping box. You must follow the current federal regulations of labeling or face a possible fine of up to $10,000 if proper labels are not in compliance.

9. Write in the amount of dry ice placed in the box on the black-and-white class "9" label. Record the weight in pounds or kilograms. Federal Express occasionally changes the weight units on the label. Record the weight in the units requested on the label. You can use the table below to convert from one unit to the other. Federal Express will return shipments which do not show the weight of dry ice.

Pounds	Kilograms	Pounds	Kilograms
10	4.4	16	7.3
11	4.8	17	7.7
12	5.3	18	8.2
13	5.7	19	8.6
14	6.2	20	9.1
15	6.6		

10. Complete the Federal Express airbill supplied by McKesson BioServices. It will already be partially completed. Enter:

    - The date of the shipment.
    - Weight of dry ice (in pounds or kilograms), as requested.
    - Number of packages and total weight of shipment.

    As with the dry ice label, record the weight requested on the label. Federal Express supplies the airbills to McKesson BioServices, and sometimes requests the weight in pounds and other times in kilograms.

    Insert the airbill in the airbill holder. See Figure 11.9 - Federal Express Airbill for Frozen Specimens.

11. To delay thawing, place the box in the -70°C freezer to wait for pick up. You don't need to do this if you pack the box within 2-3 hours of pickup and you hold the box in a controlled temperature area (for example, at room temperature and not over 80°F).

12. Notify McKesson BioServices via email (or phone if email is not possible) the day you ship the specimens. In the message, include:

    - The CC name.
    - The date of the shipment.
    - The date of expected arrival (same day or next day).
    - The airbill number from the Federal Express label.

Figure 11.8
Frozen Specimen Shipping Labels

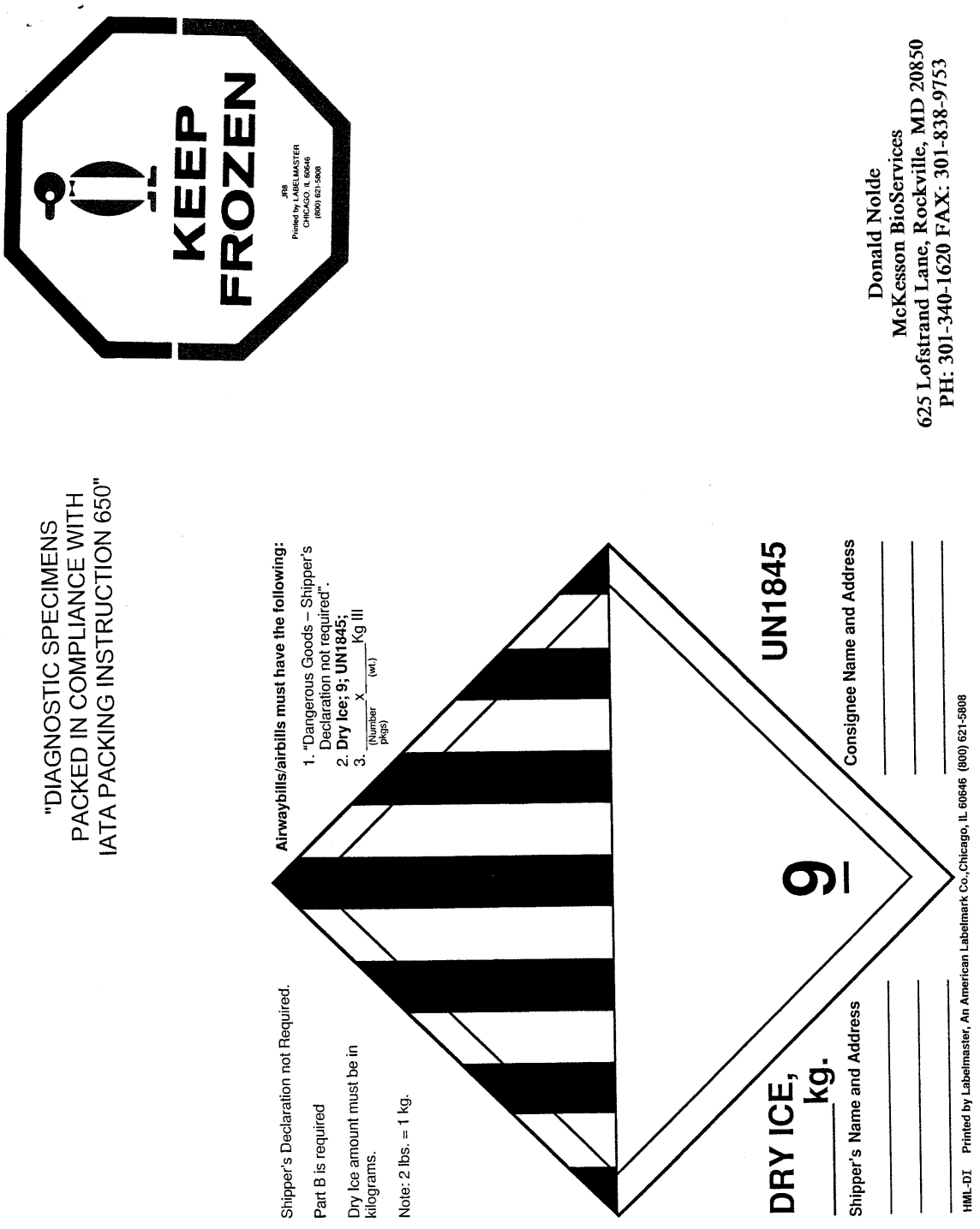
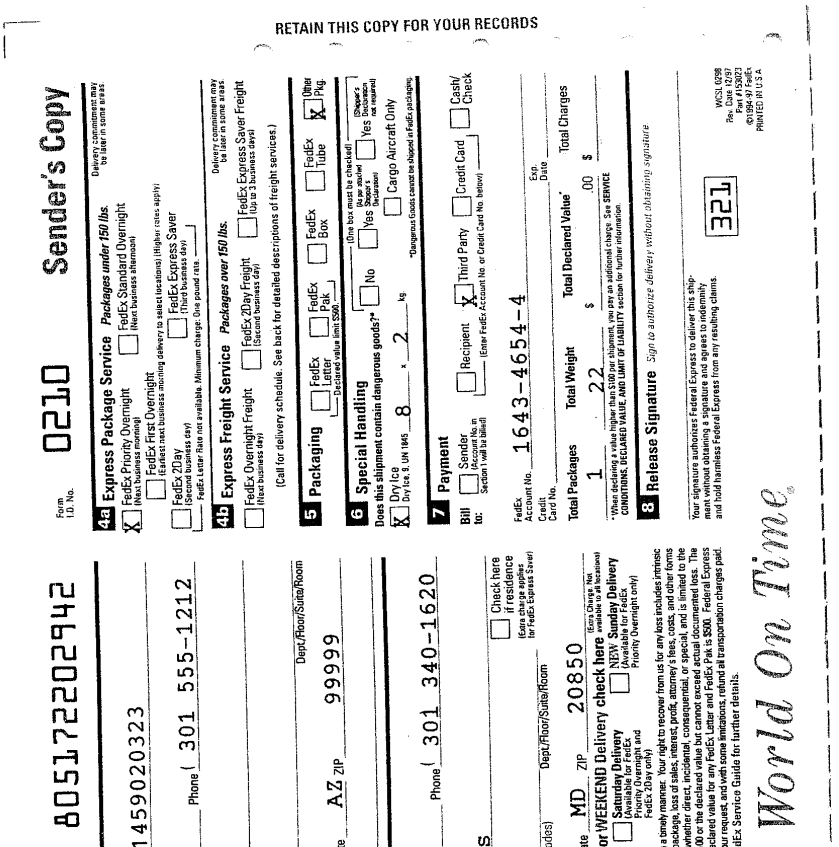


Figure 11.9
Federal Express Airbill for Frozen Specimens



11.4.3 Receipt of Frozen Specimen Shipment at McKesson BioServices

McKesson BioServices personnel will complete the Confirmation of Receipt section of the Notification of WHI Shipment form upon arrival of the shipment at the repository.

The McKesson BioServices staff will record:

- Date shipment arrived.
- Number of boxes received.
- Condition of the total shipment, for example, “thawed."

If McKesson BioServices staff do not receive the shipment on the expected day, they will trace the shipment using the airbill number.

McKesson BioServices will include a packing slip when sending blood collection and other supplies to the CC.

11.4.4 Summary of Blood Sample Shipping Procedures

1. Order dry ice.
2. Complete *Notification of WHI Shipment* form.
3. Notify McKesson BioServices of shipment by faxing them the Notification of WHI Shipment Form. Include on this form any orders for cryovials, labels, blood collection tubes and shipping supplies.
4. Pack freezer boxes in insulated shipping container with dry ice.
5. Place the insulated shipping container in the fiberboard shipping box.
6. Place Notification of WHI Shipment form in plastic bag and place in shipping box on top of the lid of the insulated shipping container.
7. Seal the fiberboard shipping box.
8. Label the box and complete Federal Express airbill.
9. Arrange for shipment.
10. McKesson will send the completed Confirmation of Receipt of WHI Shipment to the CC upon receiving the blood shipment.

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11.5 Urine Collection

Participants at the three bone density CCs will be asked to provide a clean, midstream, first-morning urine samples at selected visits during the course of the study. Collect a urine sample even if the participant has a urinary track infection.

Although the midstream clean-catch technique has been a standard practice for collecting urine specimens from participants for bacterial culture purposes, results of a recent study (New England Journal of Medicine, Vol. 328, p. 289-90, 1993) demonstrated that there was no difference in the rate of bacterial contamination between midstream urine specimens obtained and those that were obtained without prior cleansing of the perineum and urethral meatus.

11.5.1 Schedule of Urine Collection

See *Vol. 1, Table 1-A1.1 - Frequency of Data Collection* for a schedule of urine collection in CT and OS participants.

11.5.2 Urine Sample Labels

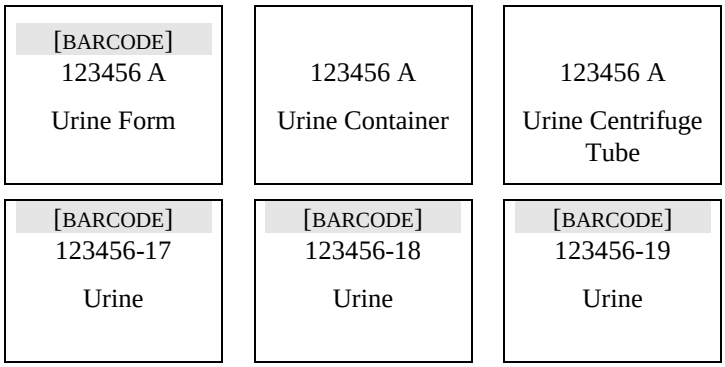
McKesson BioServices provides urine sample label sets similar to the blood sample label sets described in *Section 11.2.1 - Blood Sample Labels* . The only difference between the blood sample labels and the urine sample labels is the number of labels and the specified 2-digit cryovial numbers.

A urine sample label set consists of the following labels:

- One label for *Form 101- Urine Collection and Processing*.
- One label for the urine collection container.
- One label for the centrifuge tube.
- Three labels for the urine cryovials. Each label contains the 6-digit urine number and a 2-digit cryovial number (-17, -18, and - 19) with corresponding barcodes, and "Urine" printed on the labels. See *Figure 11.10 - Urine Sample Labels*.

Figure 11.10

Urine Sample Labels



11.5.3 Preparation Before the Visit

- Determine if the participant is to provide a urine sample.
- Label a 30 ml urine container with the participant's ID barcode label.

- Give or mail to the participant the container and instructions for collecting the urine. Instruct her on how to obtain the urine specimen by giving her the urine instruction sheet. (See

Figure **11.11** - *WHI Urine Home Collection* for the instruction sheet.)

  - During screening, mail the labeled urine container and a ziploc bag with instructions to the participant before SV1 or give to her at an SV0 visit (if your CC conducts SV0 visits). Ask her to bring in the urine sample at SV1.
  - At designated follow-up visits, mail the labeled urine container, ziploc bag, and instructions to the participant with the self-administered forms you send her before the visit.

- Attach a urine sample label set to *Form 101 - Urine Collection and Processing* and insert the form in the participant's file with the other visit packet forms.

Figure 11.11
WHI Urine Home Collection

Instructions for Home Urine Collection

- Please collect a urine sample on the morning of your visit. Collect the sample in the enclosed container and place in the ziploc bag.
- Collect the sample midstream when you first urinate in the morning sometime after 5 AM.
- Please urinate directly into the container. Fill the container about 2/3 full. If you cannot use the container, use a clean glass jar and transfer the urine into the container.

  Write the time you collected the urine on the label on the container. Put the lid on the container and put the container in the ziploc bag. Then put the container in the refrigerator or on ice until you leave for the visit.

11.5.4 At the Visit

If the participant brings a urine sample to the visit, label and complete the *Form 101 - Urine Collection and Processing* as follows:

- Attach the participant ID barcode label to the *Form 101 - Urine Collection and Processing*.
- Attach the label "Form" from the urine label set to the form and the label "Container" to the urine container the participant brought in.
- Ask the participant the time she collected the urine sample, and record the time in the appropriate place on *Form 101*.
- Take the labeled urine container and *Form 101 - Urine Collection and Processing* to the specimen processing area.

If the participant does not bring a urine sample to the visit, collect a sample at the visit. Note the number of prior voids (after 5 AM) on the *Form 101* next to the time processed. Label and complete *Form 101* as described above.

11.6 Urine Processing

1. Process the urine sample within 30 minutes of receipt. Refrigerate the specimens if they are not processed immediately. If urine is allowed to sit at room temperature, bacteria that may be present in the urine may multiply or chemicals and cells in the urine may deteriorate, causing changes in the composition of the urine.
2. Label a 15 ml conical plastic centrifuge tube with the urine sample label "centrifuge tube."
3. Transfer 10 ml of specimen from the urine collection container into the tube, screwing the cap on tightly.
4. Centrifuge for five minutes at 1,300 xg. Refer to *Section 11.3.2 - Operating the Refrigerated Centrifuge* for instructions on how to obtain 1,300 xg.
5. Label three cryovials with the cryovial labels (numbered -17, -18 and -19).
6. Transfer three 1.8 ml aliquots of urine supernatant into each of the three cryovials. Be careful not to fill past the 1.8 ml mark on the tube, as doing so may cause the tube to crack when frozen. Screw the lids onto the cryovials.
7. Complete the Urine Processing portion of *Form 101 - Urine Collection and Processing*. Mark the box corresponding to each cryovial you processed to indicate you prepared the cryovial.
8. Replace the urine container lid and discard the urine container in the biohazard container.

11.7 Freezing, Storing, and Shipping Urine Samples

1. Freeze the urine cryovials following identical procedures for freezing blood sample cryovials. See *Section 11.3.5 - Freezing and Storing Blood Cryovials* (Required). You can place the urine cyrovials in the same box as the blood cryovials.
2. Store and ship the samples following procedures for blood storage. See *Section 11.4 - Blood Storage and Shipping*. You may place the urine cryovials in the same shipment box with the frozen blood sample cryovials.

Section 11
Blood and Urine Collection, Processing and Shipment

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Figures

SECTION 12

MAMMOGRAPHY

INTRODUCTION

All Clinical Trial (CT) women are required to have baseline and regularly scheduled mammograms performed by a standard low dose radiation technique. It is recommended, but not required, that these occur at an American College of Radiology (ACR) or FDA-accredited facility and read by a qualified radiologist. Those women in the Hormone Replacement Therapy component (HRT) will have yearly follow-up mammograms. Women participating in the Dietary Modification Intervention (DM) will have follow-up mammograms in years 2, 4, 6, 8 and at close-out. Clinical Centers (CCs) have the choice to make special arrangements with one mammography facility to do all participants' mammograms or to have women continue to get mammograms through their usual source of care.

Breast ultrasounds will not be acceptable substitutes for either baseline or follow-up mammograms.

Mammograms will be classified in the ACR classification system as negative, benign, probably benign, suspicious, or highly suggestive of malignancy on *Form 85 - Mammogram*.

12.1 Timing of Mammogram

Many women interested in participating in the CT will never have had a mammogram or will have had mammograms only infrequently. These participants are likely to require a new baseline mammogram and can then be started on a schedule of annual (HRT) or every two year (DM) mammograms. These studies should precede randomization and annual visits by a period long enough for results to be available at these visits.

Some participants will have been on a regular schedule of annual or every two year mammograms before their initial screening for WHI. To allow participants to keep to their usual schedule and avoid excess radiation exposure at baseline, the protocol allows a mammogram within 12 months before Screening Visit Two (SV2) to be used as the baseline mammogram. Anniversary dates for follow-up mammograms for HRT women should, if possible, coincide with their annual visit.

If an HRT participant has been getting mammograms less frequently than every year, she must start getting annual mammograms for HRT, and they should be done no more than 6 months before the annual visit.

12.2 Scheduling Mammograms

12.2.1 Baseline Mammogram (Required)

If a woman has not had a mammogram within the 12 months before SV2, she will need to have one before Screening Visit Three (SV3). At the end of Screening Visit 1 (SV1) or SV2, schedule a mammogram appointment for her. If a woman completed a washout (which must be completed before SV1), her baseline mammogram must be no more than 12 months before that SV2. Thus, the mammogram can be done before the HRT washout begins, as long as it is not more than 12 months before the SV2.

- If you are arranging mammograms through your CC, schedule the appointment at a time convenient for the participant. It is recommended that you give her a Mammogram Appointment Card with directions to the facility, the date and time of the appointment, and any instructions your mammographer requires. (For example, some mammographers ask that women not use deodorant, talc, or other powders on the morning of their appointment. Some mammographers will supply these instructional materials for you to send or give to participants.) Let the participant know how long the mammogram is likely to take.
- Each CC can establish its own system of tracking mammogram appointments and results. This system will be referred to in this section of the manual as a Mammogram Logbook. (CCs may establish their own automated version of a logbook.)
- It is recommended that you record the date of a scheduled mammogram in your Mammogram Logbook. When a participant arranges her own mammogram appointment, ask her to call the CC when she knows the date of the mammogram. When she does call in with the date, record it in the Mammogram Logbook.

12.2.2 Follow-Up Mammograms (Required)

12.2.2.1 Annual Visit Mammograms

At least two months before an HRT participant's scheduled annual visit, begin arrangements for her to have a mammogram scheduled. Dietary Modification participants' every two year mammograms can be done at anytime during the two year interval (although WHILMA will report it as due before the appropriate biannual visit). Target anniversary dates for mammograms are based on the date of the participant's randomization. This also applies to those women who needed to complete an HRT washout. Each CC can access the *Mammogram Reminder Report* through WHILMA that will list the participants needing a mammogram. Each CC can decide on how soon before the appointment time this report should be produced. The recommended lead time is at least two months.

- Call the participant and inform her that her annual visit will be coming up and that she needs a mammogram before that time. Obtain information on where to request the mammogram report or schedule a mammogram appointment for a time that is convenient for the participant. Instruct her as per *Section 12.2.1 - Baseline Mammogram (Required)* above.
- It is recommended that you record the date of the mammogram in the Mammogram Logbook (or computer, if automated).

12.2.2.2 Annual Visit Mammograms Following a Mammogram Requiring Follow-Up in Less Than a Year

Many women, who require a 6-month follow-up mammogram after baseline, have a normal follow-up mammogram (e.g., mammogram report recommends follow-up in 12 or more months). The need for a follow-up mammogram in 6 months does not change the target date for the follow-up mammogram. For these participants, their mammogram anniversary date will remain their target annual visit date (yearly from date of randomization for HRT; dietary modification participants can maintain a flexible 2-year schedule).

12.3 Requesting and Receiving Mammogram Results

A normal mammogram report (or a normal follow-up to an abnormal mammogram) is required before you can randomize a woman into the CT or continue her study pills in the HRT. It is important to follow-up on mammogram results in an organized and timely manner, so that you do not delay randomization and can regularly address safety issues. Recommendations for timely follow-up on mammograms include:

- Provide participants with a stamped, self-addressed envelope with which the mammographer can mail results back to the CC.
- One week after the date of the participant's scheduled mammogram, check to see if a report has been received.
- If no report has been received, call the participant's mammographer and ask to have a copy of the report mailed or faxed to the CC. If you do not receive the report within one week, call the mammographer again.
- When the report arrives at the CC, log it into the Mammogram Logbook.

Complete *Form 85 - Mammogram* for each regularly scheduled mammogram report you receive. If this is a follow-up mammogram for a previous breast exam or mammographic abnormality, complete a new *Form 85 - Mammogram*. If you receive a report addendum which incorporates the review of previous films and changes the results of the original report, edit the already completed *Form 85* as needed and attach the updated mammogram report.

12.3.1 Receiving Mammograms at Unscheduled Times

If you receive a mammogram report that is not required by WHI in a particular time frame, do not fill out a *Form 85 - Mammogram* or enter it into the database. Only reports for mammograms done at the required time intervals (annually for HRT participants, follow-up studies as indicated for abnormalities found in HRT participants, and every 2 years for DM participants) should be recorded on a *Form 85* and entered into WHILMA. If, however, an unsolicited mammogram shows an abnormality and the woman is in HRT or OS (this does not apply to DM), monitor the findings closely and report them as an outcome of cancer (as appropriate) only after receipt of a final pathology report (see *Volume 8 - Outcomes*).

12.3.1.1 Lay Mammogram Reports

Data on *Form 85 – Mammogram* should be based on an actual radiology report. In October 1999, the Steering Committee approved limited use of written "lay" mammogram reports because mammographers are now required to send these more-standardized lay reports to all women. A participant may come to clinic visits with a "lay" mammogram report as proof of her mammogram. These lay reports are acceptable if they include all of the following:

- Date
- Participant's name
- Institutional letterhead
- Normal or benign findings
- Recommended mammogram follow-up is 12 months or more

If you are completing *Form 85 – Mammogram* from data on a lay report, be careful to complete only those data items that the report describes. Attach the lay mammogram report to *Form 85*.

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12.4 Actions Based on Baseline Mammogram Reports (Required)

After reviewing the mammogram report, decide if you need to take any action based on the findings. *Table 12.1 - Eligibility Based on Mammogram Results* offers recommendations for determining whether or not a woman's mammogram report makes her eligible or requires further follow-up before randomization. Clinical Centers may adopt more conservative guidelines if they wish, and, as always, clinical judgment should be used in the final decision.

12.4.1 Negative or Benign Mammogram Findings

Any descriptive findings on mammogram that do not require repeat within 12 months or referral for evaluation will be considered normal and thus eligible. Results of "mammary dysplasia," "adenosis," "fibrocystic breast tissue or disease," "coarse calcifications," or "fat-containing lymph" should be considered normal. Reports of fluid-filled cysts that are greater than or equal to 5 mm in size (and are demonstrated on ultrasound to be smooth-surfaced) or walled simple cysts can be considered normal. If there is any question regarding the nature of the cyst, even after ultrasound, a fine needle aspiration (FNA) should be performed by the woman's private physician.

Negative or benign reports may also recommend a follow-up or repeat mammogram in less than one year to assess stability. This will not exclude the woman from entering the CT or continuing with enrollment pills. However, you will need to review a report of her repeat mammogram and complete a new *Form 85 - Mammogram*, if appropriate.

12.4.2 Probable Benign Findings

A woman whose mammogram report shows a probable benign finding such as calcification with benign features, stability unknown, circumscribed mass, or cyst less than 5 mm or with irregular walls, will be considered eligible. Clinical Centers are cautioned that within this group up to 10% of these findings may represent a malignancy and should be reviewed. The CP or CC gynecologist may elect to follow participants with these results more closely and refer the participant to their private physician for further evaluation after randomization. Examples of assessing which cases may benefit from further evaluation include:

- A report of calcifications with benign features, stability unknown. In this case you have the choice of determining stability through:
  - comparing with old films or repeat the films in 6 months,
  - making a definitive diagnosis through tissue analysis, or
  - using clinical discretion to determine that the participant is indeed clear to participate in DM or HRT.

- A report of circumscribed masses. For these masses, you can:
  - refer the participant back to her primary MD to determine definitive diagnosis through tissue analysis,
  - determine stability over time by comparing with old films or by repeating the study in 6 months, or
  - use clinical judgment to determine if there would be a safety issue for this woman to participate in WHI.

If ultrasound or tissue sampling is done to confirm a benign status, document findings and procedures in the participants file. The woman may then continue in the screening process.

Table 12.1
Eligibility Based on Mammogram Results

Mammogram Results	Initial Eligibility Determination	Description	Ultrasound Requirement	Final Eligibility Determination (Enter on *Form 85 - Mammogram*, question 9 or 12, as appropriate)
1. Negative	Eligible	---	---	Eligible
2. Benign findings	Eligible	- Coarse calcification or fibroadenoma	- None	Eligible
		- Fat-containing lymph	- None	Eligible
		- Fluid-filled cysts (≥5 mm)	- Smooth-surfaced cyst walls	Dependent upon ultrasound results. May consider FNA.
3. Probably benign	Eligible	- Calcification with benign features, stability unknown	- None	Tissue diagnosis to determine benign status. (FNA may be used.) *OR* repeat mammogram in 6 months for stability.
		- Circumscribed masses	- CC discretion	Tissue diagnosis to determine benign status. FNA may be used.
		- Any cysts < 5 mm or irregular borders	- Smooth-surfaced cyst walls	Tissue diagnosis to determine benign status. FNA may be used. OR Clinical judgment by PI/MD
4. Suspicious	Temporarily ineligible		- CC discretion	Tissue diagnosis to determine benign status.
5. Highly suggestive of malignancy	Temporarily ineligible		- CC discretion	Tissue diagnosis to determine benign status.

FNA = Fine Needle Aspiration

Note: These are guidelines for results #1-3. For suspicious or high probability of malignancy results, tissue diagnosis is needed to determine eligibility.

12.4.3 Suspicious or Highly Suggestive of Malignancy Findings

A woman whose mammogram report shows suspicious or highly suggestive of malignancy results should not be randomized to the CT and should be immediately referred to her primary physician for follow-up. When the CC receives a mammogram report requiring referral, the Clinical Practitioner (CP) should notify the participant of the results and advise her to contact her primary physician. In addition, a copy of the report should be mailed or faxed to either the participant or her primary physician. It is recommended that CCs follow-up with these participants within one month to ensure that they have seen their physician.

If tissue sampling made by either FNA or open biopsy determines that there is no possible malignancy, it is recommended that the CP discuss the evidence with the PI or physician designee for concurrence. If the PI and CP agree that the abnormality is benign, complete the follow-up section of *Form 85 - Mammogram* and the woman may continue in the screening process.

12.4.4 Mammograms Requiring Short-Term Follow-Up

If a mammogram report requires a repeat film in 6 months or less, the eligibility window for baseline screening tasks may be extended for potential HRT participants only from 6 to 9 months. Since there is no safety issue for potential DM participants, those participants in whom there is a request for a short-term follow-up but are not suspicious or have a high probability of malignancy are considered eligible.

If an "Immediate/ASAP" repeat mammogram is requested on the report, the participant will be considered ineligible until cleared either by another mammogram or definitive diagnostic test (needle aspirate, ultrasound, or tissue biopsy).

For women requiring follow-up during the HRT enrollment period, dispense a second bottle of pills if needed, or stop the enrollment pills and initiate a second enrollment period when the abnormality is cleared (see *Section 15.4.1.3 - Repeat HRT Enrollment Period* for details).

12.5 Actions Based on Mammogram Reports for Randomized Women

Women randomized in the CT are required to have either yearly mammogram follow-up (HRT) or follow-up in years 2, 4, 6, 8 and at close-out (DM). Required documentation based on the reports are similar to those for baseline mammograms with the following exceptions.

12.5.1 Negative or Benign Findings

Participants who receive these findings on their follow-up reports should be informed that their mammogram was within the normal range and requires no action. They may continue with their CT activities without interruption.

12.5.2 Probable Benign Findings

HRT participants with probable benign findings should be considered on an individual basis. Most participants should be able to continue with their study pills while undergoing evaluation of the findings. However, this decision is left to each CC CP and PI or physician designee's discretion, and the option of stopping study pills during this time is available. If the study pills are temporarily discontinued, complete a *Form 54 - Change of Medication* at the time of stopping and resumption.

Call the participant to discuss the findings. If it is clinically indicated, refer her to her primary physician for evaluation. Complete *Form 85 - Mammogram* to record the probable benign findings and if a referral has been made. If follow-up studies have been performed, complete the follow-up section on *Form 85 - Mammogram.*

12.5.3 Suspicious or Highly Suggestive of Malignancy Findings

HRT participants with suspicious or highly suggestive of malignancy findings should be considered on an individual basis by each CC CP, in consultation with the consulting gynecologist and PI or physician designee, with regard to the option of stopping HRT study pills. Complete a *Form 54 - Change of* if study pills are stopped or resumed.

Call the participant to discuss the findings. Refer her to her primary physician for evaluation. Complete *Form 85 - Mammogram* to record the suspicious or highly suggestive of malignancy findings and document that a referral has been made. Call the participant within a month to confirm that she has made contact with her primary physician. If appropriate documentation is obtained confirming benign status, complete the follow-up section on *Form 85 - Mammogram*.

If a participant refuses any diagnostic follow-up tests and/or exams for an abnormal breast finding, stop her study pills. Study pills may be resumed if the participant does have the required test or exam and abnormal findings are not cancerous. Complete *Form 54 – Change of Medications* when you make such study pill changes.

If investigation of a mammogram abnormality leads to the diagnosis of carcinoma in-situ or cancer, initiate the following steps:

- Contact the participant and refer her to her primary physician for evaluation.
- Advise HRT participant to <u>permanently discontinue HRT study pills immediately</u> and return the bottles at the next possible visit or provide her with a stamped self-addressed mailing envelope.
- Complete *Form 85 - Mammogram* to indicate initial report findings and follow-up findings.
- Initiate outcomes investigations for both HRT and DM participants. (See *Volume 8 – Outcomes*.)
- Complete *Form 7 - Participant Status* to indicate the reason for change of status in the intervention.

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Mammography

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SECTION 13

ECG PROCEDURES

INTRODUCTION

Standard 12-lead ECGs are obtained at baseline for all Clinical Trial (CT) participants. This will enhance the accuracy of estimating the prevalence of cardiovascular disease (CVD) in the study population and characterize the cardiovascular status regarding conditions such as left ventricular hypertrophy and cardiac arrhythmias. See *Figure 2.1 - Frequency of CC Tasks* for schedule of ECGs at follow-up visits.

A standard 12-lead ECG (12 SL ECG) is performed in a supine or semi-recumbent position for all participants. The safety and comfort of the participant are the highest priorities. The MACPC electrocardiograph is used to record the ECGs and transmit the readings to the ECG Center for diagnostic classification.

Extra effort is required to achieve accurate electrode placement than in routine clinical ECG laboratories, and to reduce the occurrence of incorrectly connected electrodes *(lead reversals*). In the event of inadequate ECG quality (grades 4 or 5), immediate corrective action is needed to correct technique. See *Form 311 - ECG Quality Assurance Checklist*.

13.1 General Requirements and Set-Up

13.1.1 Storing Supplies

Storing the ECG Paper

The thermal paper used in the MACPC can be stored for an indefinite period of time with the following precautions. These precautions apply to both unused paper and to paper that has already been run through the MACPC printer.

- Store the thermal paper in a cool, dry, and dark place, where the temperature is below 27.6°C (80°F) and the relative humidity is between 40% and 65%.
- Do not store thermal paper in a location where it will be exposed to bright light or ultraviolet sources such as sunlight, fluorescent light, or similar lighting. Ultraviolet light causes yellowing of paper and fading of tracings.
- Avoid contact with cleaning fluids and solvents such as alcohol, ketone, ester, ether, etc.

Storage of Adult Disposable Electrodes

The adult disposable electrodes are made with a unique conductive adhesive hydrogen. Their performance may be adversely affected if individual cards of electrodes are exposed to air or liquids for long periods of time. Always store unused cards of electrodes in their pouch or in a sealable plastic bag. Store unopened products in a cool, dry place.

13.1.2 MACPC Description

The MACPC is a widely used piece of equipment approved by the Underwriter's Laboratory and represents the most advanced technology in electrocardiography. In a matter of seconds, the MACPC is capable of delivering a complete computerized analysis of an ECG, both in morphology and rhythm.
For WHI, you will use the MACPC to obtain and store data before transmitting it to the ECG Center. The MACPC can store up to 12 ECGs before transmission. Complete instructions for operating the MACPC are provided with your machine. Read the manual thoroughly and become familiar with your model machine.

Equipment Precautions

The MACPC Unit is grounded so that the risk of electrical shock is highly unlikely. However, if at any time a "short" occurs or you discover frayed wiring or a potentially dangerous situation, do not use the equipment. Do not attempt to remove the cover or back of the unit. Notify your supervisor immediately of any equipment malfunction or damage.
The safety of the participant during the recording is of utmost importance.
Clean the ECG equipment at regular intervals. Use a dust-free cloth to clean the keyboard and the liquid crystal display.

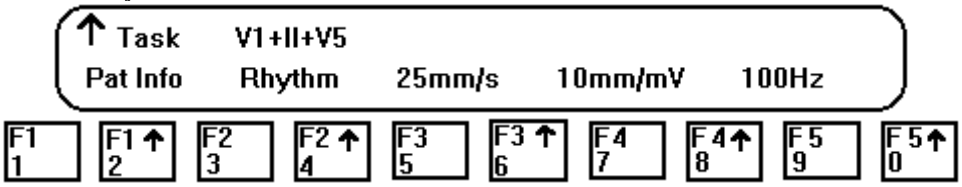
13.1.2.1 MACPC Keyboard Description

The Liquid Crystal Display (LCD) is on the top part of the MACPC keyboard and is used for entering information and displaying messages. The keyboard descriptions listed in the following sections correspond to the MACPC keyboard pictured in *Figure 13.1 - Liquid Crystal Display and Keyboard Description.*

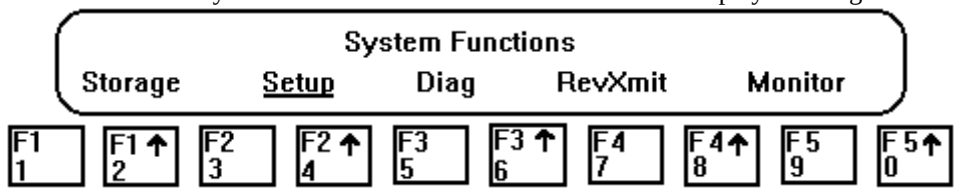
Function Keys

Notice that the keyboard has a set of 10 numerical keys. Each key has a letter F with a number from 1 to 5 on it (**F1, F2, F3, F4 or F5**), as well as a single number (1, 2, 3, 4, 5, 6, 7, 8, 9, 0). The keys serve as dual-

purpose keys. The keys are used to type in numerical data or to select an item from the LCD display. For example, in the *Main Menu* display below, pressing either the **1** or **2** key would select the *Pat Info* function because that *Pat Info* is directly above these two keys.



The *Task* function, on the other hand, appears next to an arrow in the display. To select this function, press the **SHIFT** key  and either the **1** or **2** key at the same time. This causes *Main Menu* display to change to:



If you press the 1 or 2 key now, then you would be selecting *Storage* since the *Storage* function is directly above these two keys.

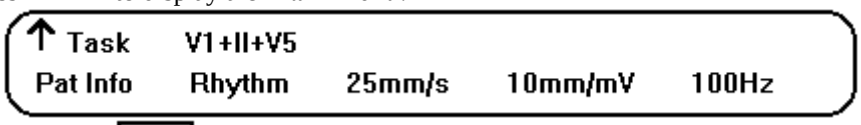
Figure 13.1
Liquid Crystal Display and Keyboard Description

THIS FIGURE CAN BE FOUND IN I:\MOP\VOL2\FIG13-1.DOC

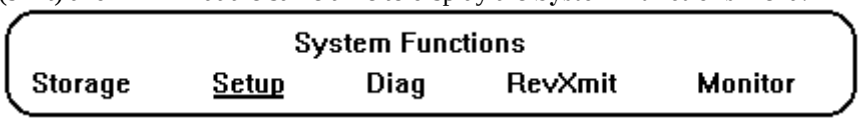
13.1.2.2 MACPC Set-Up

(See Marquette MACPC Operator's Manual, Chapter 12 - Cart Set-up for further information.)

To begin set-up, press  to display the **Main Menu**:



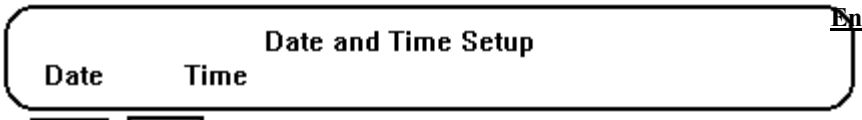
Next, press  (shift) and  at the same time to display the **System Functions** menu.



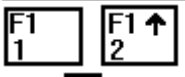
Follow the steps below to set up the MACPC. Repeat the steps any time you need to reset the MACPC, for example, after running out of power.

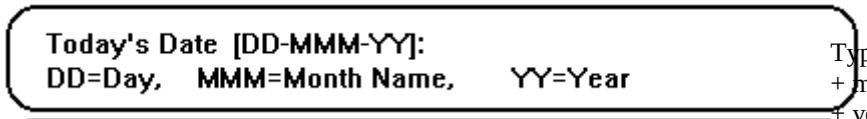
13.1.2.3 Date and Time Set-Up

Select **Setup** (F2) by pressing either  or  to set the date and time. The following display will appear if a Level 1 password has been entered: [Enter L1 (password) press return.]

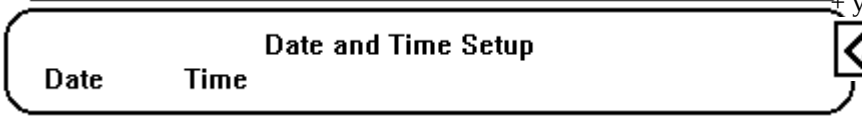


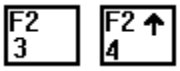
Enter:





Type day + dash + month + dash + year and press  (return).





Press either 3 or 4.

Enter:
Type hour + dash + minute and press ↵.

```
Time (HH-MM)
HH=Hour,    MM=Minute    (24 Hr Clock)
```

```
Date and Time Setup
Date    Time
```

Press ⊘ (stop) to return to the *Main Menu*.

13.1.2.4 Phone Set-Up

```
Cart Setup
Dat/Tim    Phone    LdGrps    Reports    More
```

F2 3 F2 ↑ 4

Press either 3 or 4.

```
Phone Number
 0-9 # * = ,
```

*Type phone number. Then press ↵.

* The # and * signs are touch-tone symbols.
The "," sign provides a 2-second pause and may be used repeatedly for longer pauses. (For example, in the phone number 1,,,8082345 there will be a 6-second pause between the 1 and 8 numbers when dialing.)
The "=" sign is used to wait for a dial tone. (For example, in order to dial an outside number, your phone system may require you to dial 9 before dialing the 7-digit phone number. In this case, you would type in 9 = before the 7 digits. A sample number would look like this: 9=1234567.)
You may need a telephone repair person to arrange a direct line to the ECG Center's transmission number (910) 716-0837. This often occurs when an authorization number is needed to obtain an outside line.

Press ⊘ (stop) to return to the *Main Menu*.

13.1.2.5 Miscellaneous Set-Up

See Marquette MACPC Operator's Manual, Chapter 12 - Cart Set-up for further information.

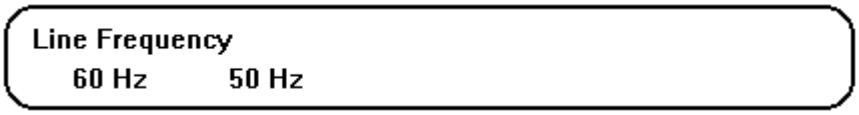
To complete MACPC set-up follow this format:

Enter:

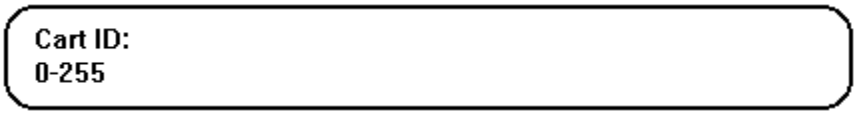
1.
```
Cart Setup
Dat/Tim    Phone    LdGrps    Reports    More
```
More

2. 

Misc

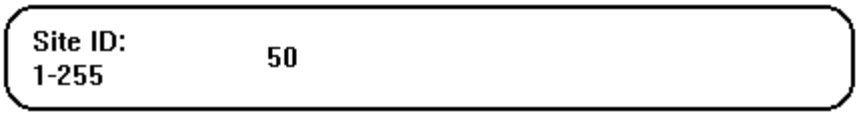
3. 

60 Hz

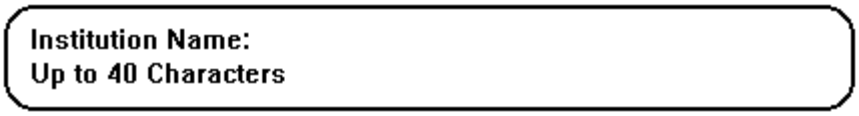
4. 

11 BETTENDO	**24 MEMPHIS**	**47 HOUSTON**	**61 CINCINNA**
12 BIRMING	**25 MINNEAPO**	**48 WORCESTR**	**62 DETROIT**
13 BOWMAN	**26 NEWARK**	**49 NY-CITY**	**63 IRVINE**
14 BRIGHAM	**27 PHOENIX**	**50 COLUMBUS**	**64 MIAMI**
15 BUFFALO	**28 PITTSBUR**	**51 MEDLAN**	**65 NEVADA**
16 CHICAGO	**29 TUCSON**	**53 OAKLAND**	**66 PORTLAND**
18 SEATTLE	**30 UCDAVIS**	**54 JACKSONV**	**67 SANANTON**
19 ATLANTA	**42 STANFORD**	**55 TORRANCE**	**68 LA**
20 EVANSTON	**43 MILWAUKE**	**56 MADISON**	**69 FALLRIV**
21 IOWACITY	**44 GWU-DC**	**57 STONYBRK**	**70 MEMSAT**
22 LAJOLLA	**45 HONOLULU**	**58 CHAPHILL**	**71 RRC**
23 PAWTUCK	**46 GAINESVI**	**60 CHI-RUSH**	**72 NEWBRUNS**
			73 DESMOINE

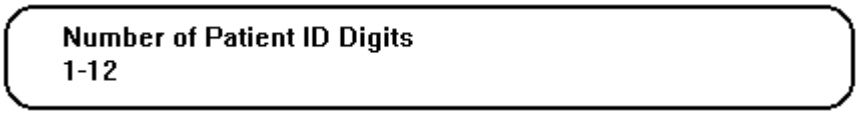
Very important steps!!!

5. 

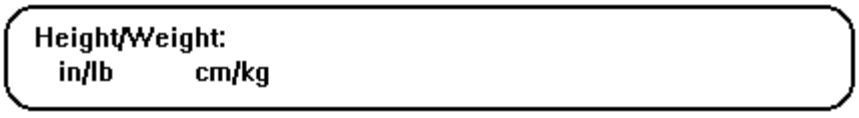
"50" identifies the ECG as belonging to WHI

6. 

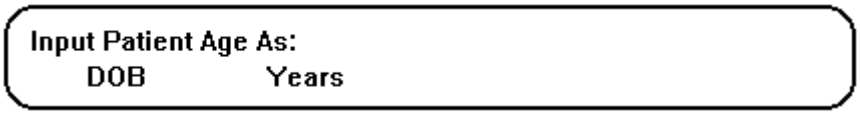
Type your own Institution Name/State

7. 

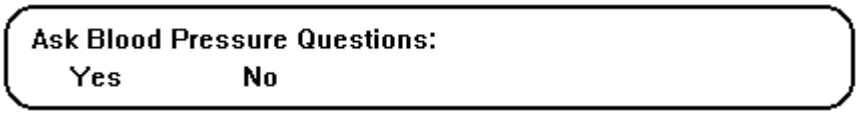
7

8. 

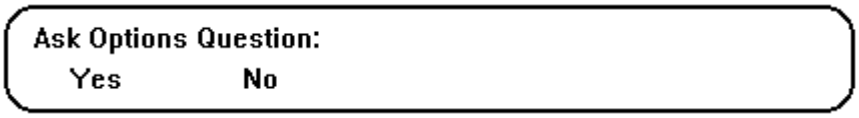
cm/kg

9. 

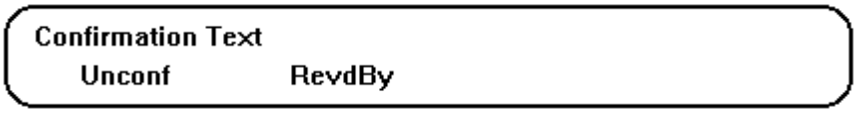
Years

10. 

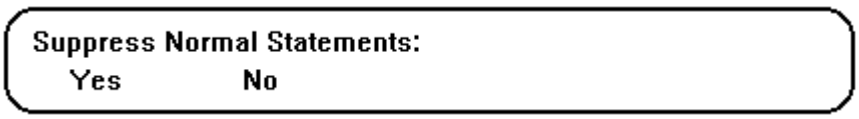
No

11. 

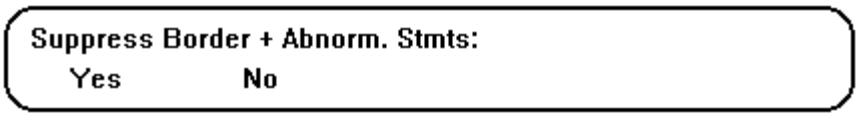
No

12. 

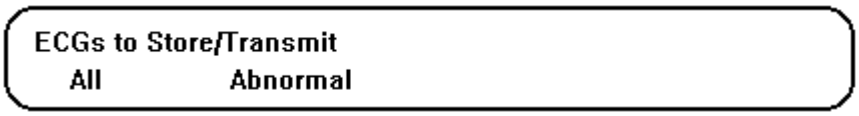
Unconf

13. 

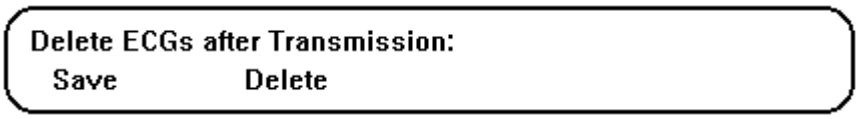
Yes

14. 

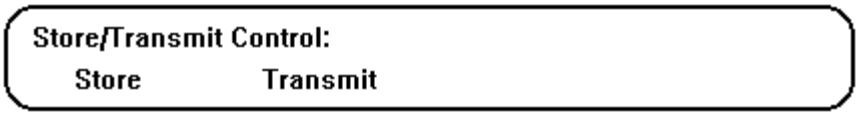
Yes

15. 

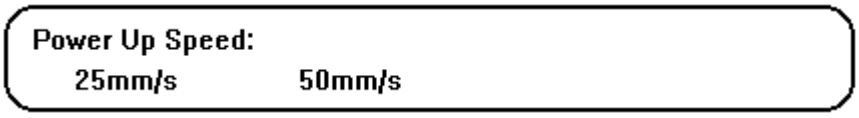
All

16. 

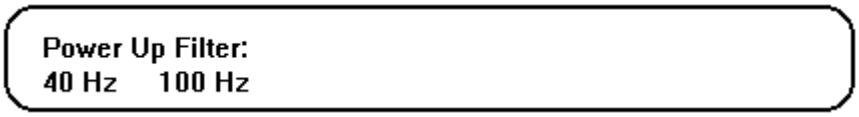
Save
(After transmission print a directory, then manually delete all ECGs.)

17. 

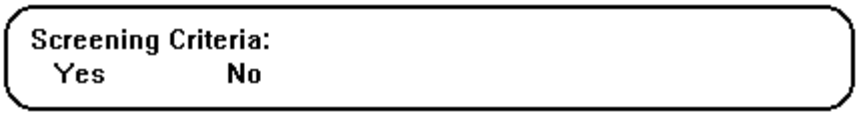
Store until you need to transmit.

18. 

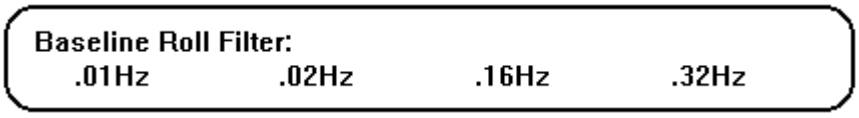
25mm/s

19. 

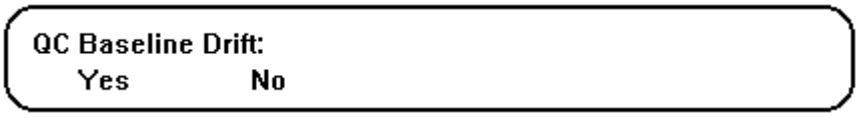
100 Hz

20. 

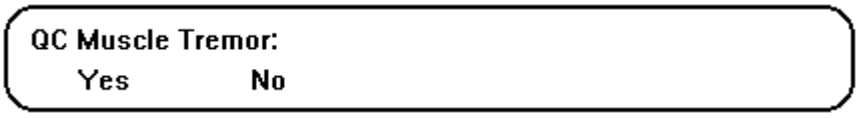
No

21. 

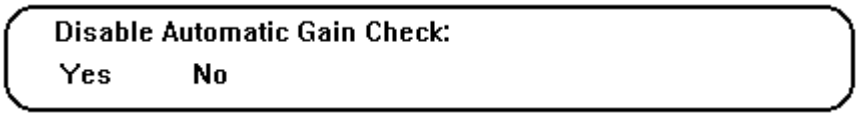
.16Hz

22. 

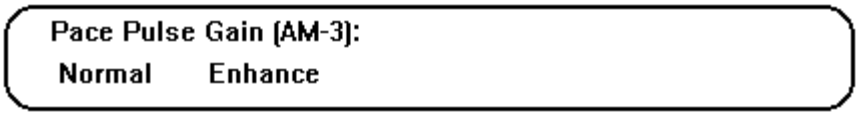
No

23. 

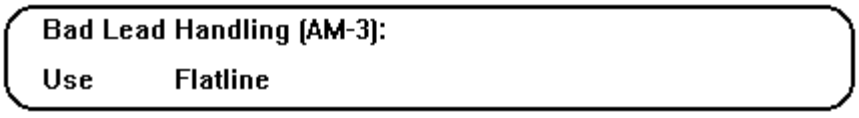
No

24. 

No

25. 

Normal

26. 

Flatline

27. 

Press  (stop) to return to Main Menu

13.2 Preparing for ECG Recording

The bed for ECG recording must be stable and properly supported. A stepping stool should be provided for safety if there is not a step with the table. Maintaining the participant's safety is imperative. The ECG technician needs to be attentive to special disabilities that may cause serious injuries, especially for older women (hip fractures, etc.).
Make sure that the legs of the exam table are seated firmly on the floor (or on holders if a folding type of bed is used). Place a pillow at the head of the exam table and cover it with clean examination paper. The participant can be supine (flat on her back) or semi-recumbent.

1. Check the following:
   - Clean sheets or examination paper are on table/bed.
   - Bed is wide enough to support the participant's arms comfortably.
   - Participant is comfortable and relaxed.
2. Introduce yourself:
   - Ask the participant to relax, and explain a bit about what you are going to do, for example:

     "Have you ever had an electrocardiogram recorded before?"
     "It does not hurt, so just relax."
     "This will not take long—less than ten minutes."
   - Explain why we are doing this:

     "We are trying to learn more about heart disease in women."
3. Ask the participant to undress to the waist and put on a gown with the opening in the front. Ask her to sit or lie in a supine or semi-recumbent position on the recording bed with shoulders straight and arms relaxed at the sides.
4. Keep the participant covered as much as possible during lead placement and close the gown opening in front when lead placement is completed.
5. Ask her to avoid movements which may cause errors in marking the electrode locations, but encourage her to talk.
6. Use a bed that is wide enough to properly support her elbows.
7. Use felt tip pens or wax pencils for marking chest electrode locations.
8. Wipe the general area of each electrode position with an alcohol prep to remove skin oil and perspiration.

13.2.1 Limb Lead Electrode Placement

To assure comparability of data, follow the uniform procedures for electrode placement, skin preparation, and quality assurance below. Refer to *Figure 13.2 - Placement of Limb Leads* for placement of the leads.
Note: Electrode positions in women are determined with respect to anatomical landmarks on the thorax. In women with large pendulous breasts, leave breast in place while placing electrodes. Gently move the breast if participant appears uncomfortable with electrode placement.

1. Begin with the RIGHT LEG. This is an important connection as it is the ground connection. A careless skin electrode connection here will influence all ECG leads. Mark a dot or X with a marker on the inner side of the right leg. Use firm circular motions with the alcohol gauze, rubbing about ten times or until skin becomes red. For women with dark skin, rub ten times.
2. Repeat this procedure for the RIGHT ARM.

3. LEFT LEG. Prepare the skin, and mark the position.
4. Repeat this procedure for the LEFT ARM.
5. Place the limb electrodes on the four sites prepared and marked. The connector edge of the electrodes should face up towards the head. Do not connect the electrode cables until you have completed locating and preparing the chest electrodes.
6. Use of the newest type disposable silver chloride electrodes is highly recommended for hygiene, easy application and removal after recording, and ECG quality. These disposable electrodes do not need electrode paste.
7. If the participant has an amputated limb, place the electrode on body part closest to that limb. For example, in amputated arms, place electrode near shoulders; and in amputated legs, place electrodes above the hip. See *Figure 13.2 - Placement of Limb Leads*.

Figure 13.2
Placement of Limb Leads

THIS FIGURE CAN BE FOUND IN I:\MOP\VOL2\FIG13-2.DOC

13.2.2

Locating Chest Electrodes

Refer to *Figure 13.3 - Anatomy of the Sternum, Figure 13.4 - Anatomic Structure of the Thorax,* and *Figure 13.5 - Location of Chest Electrodes* for placement of the chest electrodes and to the Heart Square in *Figure 13.6 - Heart Square.*

1. Location of electrodes V1 and V2.

   Standing on the left side of the participant, locate the sternal angle (where the manubrium joins the sternum) firmly in between the index and middle fingers of your right hand at the mid-sternal line. Move your fingers along the sternal angle laterally to the right sternal border. This is where the second rib joins the sternum. Locate the second rib firmly in between your two fingers. You now have your index finger in the second intercostal space at the right sternal border. Replace your index finger position by your middle finger and move your index finger to the third intercostal space. Make sure that you feel the third rib in between your two fingers. Replace the position of your index finger by your middle finger and move your index finger to the fourth intercostal space at the right sternal border. Your index finger is now at the location of V1. Make an X with your pen.

   Now locate V2 at the level of V1 at the left sternal border. Feel the fourth intercostal space there firmly and mark V2 location with your pen.

   At this point, mark a dot in the midsternal line in between V1 and V2. This mark will serve as a reference level for V1 and V2 and the fourth intercostal space in case you lose the location marks of V1 and V2 during skin preparation.

2. Location of the horizontal reference level for electrodes V4, V5 and V6 (point E).

   Starting from the V2 location, keep the middle finger of your right hand firmly in the fourth intercostal space and move it laterally and slightly diagonally downwards in the fourth intercostal space towards the nipple. Feel the fifth rib with your index finger and move your middle finger to the fifth intercostal space. Move your finger in the fifth intercostal space laterally to where the left midclavicular line intersects the fifth intercostal space. (The midclavicular line starts where you feel a bend in the clavicle. The midclavicular line is like a longitude line on the globe at a 45 degree angle towards the center of the thorax.) Now mark the exact transverse (horizontal) level of the point of intersection of the midclavicular line with the fifth intercostal space at the midsternal line below V1 and V2. It will be approximately one inch below the dot between V1 and V2. This is E. It is a reference level for the locations of V4, V5 and V6.

3. Location of electrode V6.

   Move the participant's elbow laterally away from her body. Note the starting point of the left midaxillary line halfway between the axillary folds formed by the anterior and posterior axillary lines. Follow the midaxillary line in the exact vertical center plane of the thorax down to the intersection of the horizontal plane marked by the location of E. This is the exact location of the V6 electrode. Note that it is a common mistake to locate the midaxillary line too far anteriorly, towards V5 location.

4. Location of V4, V5, and V3 electrodes and Heart Square Measurements.

   The Heart Square accommodates all expected dimensions of thorax diameters. It simplifies the procedure by eliminating the need for calculating the difference between E and V6 measurements.

   - Place the Heart Square firmly on the lower sternum at position E (see *Figure 13.6 - Heart Square*). Verify that the E and V6 arms of the Heart Square are exactly horizontal and vertical in the horizontal plane of the thorax at the level of the E position. (If the Heart Square does not slide easily, a small amount of a lubricant, such as WD-40, can be used. Lubricant must not come in contact with skin.)

- Slide the V6 arm of the square so that the arrow pointing to V6 is exactly at the marked V6 location
  (0 cm arrow on V6 arm).
- Read measurement at E to the nearest 0.5 cm. Identify this same number along the V6 arm and follow the corresponding 45° line to mark V4 position. (See *Figure 13.5 - Location of Chest Electrodes*.)
- Record the E measurement in the ECG Recording Log, dropping the decimal point (e.g., 14.0 cm. = 140). Record the V6 measurement (at the V6 scale where it intersects the E arm) as you do for the E measurement. (e.g., 7.0 = 070.)

- Proceed to mark location V3, which is equidistant between V2 and V4, and V5, which is equidistant between V4 and V6.

- Enter measurements on *Form 91 - ECG Log Sheet* as follows:
  e.g. E = 140 in the Height field (three digits)
  V6 = 070 in the Weight field (three digits)

Wash Heart Square with gentle soap and warm water (one part detergent to 10 parts water) after each participant is measured. Gently wipe dry with a soft cloth. Lubricate as necessary. Do not drop the Heart Square.

13.2.2.1 Locating Chest Electrodes in Large Chested Women

Women who have a BMI of >40 may have a chest width greater than the Heartsquare can accomodate. In these situations, use the following guidelines for lead placement:
1. Follow instructions given in section 13.2.2 - *Locating Chest Electrodes* to determine location of V1, V2, V4, and V6 (point E).
2. Keep the Heartsquare strictly horizontal and vertical in the reference frame of the thorax at the level of E and V6 . Use a steady and firm pressure against soft tissues.
3. Make a mark on the participant at the last Heartsquare measurement. (The last marking available on the Heartsquare arm for either E or V6 arm.)
4. Use a tape measure to measure this distance (in centimeters) between the last Heartsquare marking and the actual E or V6 mark on the participant.
5. Add this distance to the initial E or V6 readings for the correct values and record them in the appropriate "Height" and "Weight" columns respectively of your log.
6. To locate V2-V5 lead sites, measure the distance between E and V6.
   - V4 will be located at the midpoint in the horizontal plane of E and V6.
   - V3 will be located at the midpoint between V2 and V4.
   - V5 will be located at the midpoint between V4 and V6.

   NOTE: V2, V3, and V4 must be on a straight line in a 45 degree angle to midsternal line. V4, V5, and V6 should be on a straight line in the same plane as E.

Figure 13.3
Anatomy of the Sternum

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Figure 13.4
Anatomic Structure of the Thorax

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Figure 13.5
Location of Chest Electrodes

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Figure 13.6
Heart Square

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13.2.3 Skin Preparation for Chest Electrodes

Rub each chest electrode location briskly with alcohol and gauze (or sandpaper wipes) in a circular motion up to 10 times or until the skin becomes slightly red. This removes dead skin and oil.
If the rubbing of the skin removes the marks of electrode locations, remark each location. Never rub location E or the spot between V1 and V2. Use these as landmarks for remarking V1 and V2, V4 and V6, and finally, V3 and V5, in that order.
Place electrodes now in their sites in the order V1, V2, V3, V4, V5 and V6.

13.2.4 Attachment of Electrode Cables

The optimal sequence of electrode cable connecting is determined by the design of the ECG Acquisition Module of the MACPC. Follow the same order to minimize the risk of wrong connections (lead reversals). *Figure 13.7 - Acquisition Module 3 (AM3)* and *Figure 13.8 - Acquisition Module 4 (AM4)* indicate two different types of acquisition modules for the MACPC. AM3 facilitates connecting leg electrodes first (RL, LL, RA, LA). AM4 facilitates connecting RL, RA, LL, LA. Most CC sites will have AM4 modules.
Start by placing the ECG Acquisition Module on the participant's left side or lower chest. (Place a small towel under the module for participant comfort.)
The correct sequence for connecting the electrode cables is:

1. Right Leg (RL)
2. Right Arm (RA)
3. Left Leg (LL)
4. Left Arm (LA)
5. V1
6. V2
7. V3
8. V4
9. V5
10. V6

Make sure that you do not mix up what is your right and left and what is the participant's right and left. This happens easily and more often than you think.
Electrode cables should come in reasonably straight lines along the body toward the electrodes. Avoid looping cable wires. Place wires so that there is as little tension as possible on the electrodes.
With disposable electrodes, the silver dot on the connecting wire must touch the electrode. In newer models of the MACPC, this is facilitated by an alligator clip with a button on the top side and the silver dot on the down side.

Figure 13.7
Acquisition Module 3 (AM3)

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Figure 13.8
Acquisition Module 4 (AM4)

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13.2.5

ECG Preparation Summary

*Table 13.**Error! Bookmark not defined.**. - ECG Preparation Summary* lists the steps and sequence to follow in locating and marking the electrode sites, skin preparation, electrode placement, and electrode cable attachment.

Table 13.1
ECG Preparation Summary

A.	Locate and Mark	1. RL 2. RA	3. LL 4. LA
B.	Prepare Skin	1. RL 2. RA	3. LL 4. LA
C.	Attach Electrodes (connector facing head)	1. RL 2. RA	3. LL 4. LA
D.	Locate and Mark	1. V1 2. V2 3. Spot between V1 and V2 4. E 5. V6 6. V4 using Heart Square Measurement 7. V3 8. V5	
E.	Prepare Skin and Re-mark Locations	1. V1 2. V2 3. V3	4. V4 5. V5 6. V6
F.	Attach Electrodes (if disposable electrodes)	1. V1 2. V2 3. V3	4. V4 5. V5 6. V6
G.	Connect Electrode Cables to Limb Leads	1. RL 2. LL	3. RA 4. LA
H.	Connect Electrode Cables to the Chest Electrodes	1. V1 2. V2 3. V3	4. V4 5. V5 6. V6
I.	Verify one by one that the connections to all electrode sites are correct. Recognize the letter code on the cable before connecting each electrode.		

13.2.6 Registering Participant in the ECG Log

Before recording the tracing, record the following information on *Form 91 - ECG Log*. Remember to write in your CC number on each log sheet. (The name in parenthesis is the name of the MACPC field into which you will enter the data.)

- Date of Recording
- Participant's Last Name
- Participant's First Name
- First 7 Digits of Participant's ID Number
- Last Digit (character) of Participant's ID Number
- Baseline or Follow-up number (Location Number field):

Screening Visit	00
AV3	01
AV6	02
AV9	03
Closeout	04

- Technician Staff ID (Room Number field)
- Participant's Age
- Measured E Value (Height field)
- V6 Measurement (Weight field)

13.2.7 Entering Participant ID

For each tracing, enter the following information into the MACPC from *Form 91 - ECG Log* in the order listed.
Select "Pat Info" by pushing 1 or 2. For several items the MACPC message does not correspond to the value you should enter. The list below gives the MACPC message followed by the value to enter in parenthesis.

	MACPC Message (WHI Value)	**Enter**
1.	New Patient	Yes/No
2.	Patient's Last Name **(Acrostic)**	Enter first four letters of the last name only. If the last name is less than four letters, use asterisks at end of name to complete four characters.
3.	Patient's First Name **(Check digit)**	Enter the last digit (a letter) of the participant's ID number.
4.	Patient's Identification Number	Enter first seven digits of participant's ID number.
5.	Referred by	Enter WHI
6.	Location Number **(Baseline or Follow-up Number)**	Enter follow-up number (see list in *13.2.6 - Registering Participant in the ECG Log*

7.	Room Number **(Staff ID)**	Enter 3-digit WHI employee number.
8.	Patient greater than one year of age	Yes.
9.	Age	Enter participant's age in years (2 digits).
10.	Height **(E value)**	Enter E measurement (3 digits, no decimals).
11.	Weight **(V6 measurement)**	Enter V6 measurement (3 digits, no decimals).
12.	Sex	Enter female.
13.	Race	Press Enter. (Answer not necessary for WHI.)
14.	Medications	Press Enter. (Answer not necessary for WHI.)

13.3 Recording the 12-Lead ECG

Ask the participant to relax, breathe normally and to remain still (without talking) while the tracing is recorded.
Record the ECG following the instructions and the format provided in the Marquette MACPC Operator's Manual, Chapter 3 - Taking a Resting ECG.

13.3.1 Error Messages

Observe the display panels on the MACPC for indication of an error, either a lead reversal, poor quality, or a missing signal from a lead. Common problems are listed in *Section 0 - 13.3.2 Quality Check After* Recording below. *Chapter 15 - Troubleshooting* in the Marquette MACPC Operator's Manual gives a listing of other possible messages. If any of the listed displays occurs, the problem should be corrected before transmission to the ECG Center.

13.3.2 Quality Check After Recording

It is extremely important that the electrocardiograms have a clean baseline and are free of drift, muscle tremor, and A-C interference. Enough variables influence the tracing without introducing unnecessary technical ones. It is the responsibility of the examiner to produce high quality ECGs, using uniform techniques from tracing to tracing every day. ECGs will be given a quality grade of 1-5. Grades of 4 and 5 are not acceptable.
After running, inspect the ECG record immediately for quality. Repeat the ECG recording if you spot any quality problems.
Use the following checklist to identify any potential problems:

1. Excessive baseline drift in any lead.

   Drift in excess of 1 mm between baseline points (QRS onset) of any two successive complexes is a sign of excessive drift (see *Figure 13.9 - Excessive Baseline Drift*). This often occurs with poor skin preparation.

2. Excessive muscle noise.

   Random noise in excess of 1/2 mm may cause coding problems and requires a repeated recording (see *Figure 13.10 - Excessive Muscle Noise*).

3. Motion artifacts, loose electrode contact, or electrodes falling off. These may cause sudden jumps in some ECG leads (see *Figure 13.11 - Motion Artifacts or Loose Electrode Contact*).

   Electrodes falling off is common particularly when electrodes are placed on hairy arms or legs; loose skin can also be a problem and certain precautions can save time.

   1. Establish a good connection by parting the hair before attaching the electrode.
   2. Lay a towel across the wires to prevent the weight of the wire from tugging at the electrode. A twisted wire may tend to pull at the electrode. If necessary, re-position the electrode by slightly adjusting the angle of the clip away from the patient-cable box.
   3. It may be necessary to tape down the electrodes on the arms and legs of participants with extremely hairy arms and legs.

4. Excessive 60 Hz noise.

   Periodic 60 Hz noise visible in the record is often associated with poor skin-electrode contact, participant not being relaxed, or unfavorable recording location. The latter can be caused by A-C interference from nearby machines and is a common problem in a CC or hospital setting. It can be caused by poor

electrode contact or interference from nearby equipment. The technician should try different instructions from Chapter 15 - Trouble-Shooting Guide in the MACPC Operator's Manual to track down the source of the interference. Watches, eye glasses, rings, or bracelets do not cause interference. Make a visual check of this before recording.

5. Possible lead reversals.

   Look for normal progression of chest lead patterns from V1 to V6. Normal progression of QRS-T patterns does not occur in many abnormal conditions but the absence of normal progression always warrants ruling out possible electrode reversal problems. Most common lead reversals involve leads V2 and V3, V3 and V4, V1 and V3 (see *Figure 13.12 - Lead Reversal, V1-V3*), and left arm/right arm. LA/RA lead reversal is easy to spot (*Figure 13.13 - Lead Reversal, LA-RA*) and should be suspected if P, QRS and T are all mainly negative in lead I.

   Lead reversals such as RA-RL reversal are difficult to detect and can cause critical diagnostic classification errors. They often go unnoticed. Therefore, the procedures recommended for double-checking electrode lead connections are extremely important (see *Table 13.1 - ECG Preparation Summary* in *Section 0 - ECG Preparation Summary* above). The expected incidence of true CVD events in the trial is fairly low.

Figure 13.9
Excessive Baseline Drift

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Figure 13.10
Excessive Muscle Noise

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Figure 13.11
Motion Artifacts or Loose Electrode Contact

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Figure 13.12
Lead Reversal, V1 - V3

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Figure 13.13
Lead Reversal, LA-RA

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13.3.3

Post-Examination Procedures

1. Remove the tracing from the MACPC.
2. Remove the lead wires and electrodes. Care should be taken when removing electrodes since this procedure can cause some discomfort and skin irritation. You may apply body cream after the ECG recording if the participant's skin appears irritated after removal of electrodes.
3. Place the lead wire cable in a protective covering and store in the carrying case overnight.
4. Turn off the MACPC unit at the end of the day by pressing the power switch located on the right lower side of the keyboard.
5. Complete *Form 86 - ECG*.
6. Place the ECG tracing in the participant's file flagged for CC physician review. If the quality of the ECG does not meet the standard evaluation criteria, repeat the ECG at the next possible visit.

13.3.4 Definition of Alerts

You are not expected to be able to interpret ECGs. However, you need to familiarize yourself with interpretative statements printed on the ECG hard copy by the 12SL ECG analysis program of the MACPC. These alert conditions include situations that may warrant referral because of the possibility of acute (new) cardiac injury (myocardial infarction) and certain arrhythmic events or cardiac conduction problems that may call for therapeutic actions.

The 12SL ECG program should be considered a screening device that tends to be overly sensitive. Most of the interpretive statements such as "non-specific repolarization abnormalities" or even "myocardial infarction - age undetermined" are not considered acute events needing referral.

The following conditions are immediate and urgent alerts (as noted) identified in the protocol (see *Vol. 1 - Study Protocol and Policies, Section 1 - Protocol, Section 5.5.5.1 - Immediate and Urgent Referrals*). Refer to the referenced figures in this section for examples. (Individual CCs may establish additional alert conditions.)

- Heart rate $\leq$ 40 beats/min. (see *Figure 13.15 - Sinus Bradycardia*), or $\geq$ 130 beats/min. (See *Figure 13.17 - Sinus Tachycardia $\geq$ 130 bpm* and *Figure 13.18 - Sinus Tachycardia $\geq$ 140 bpm*; **Urgent**).
- Sustained ventricular tachycardia. (**Immediate**)
- Ventricular pre-excitation mobitz type II AV block, or Wolff-Parkinson-White (WPW) ECG pattern. (*Figure 13.19 - Ventricular Pre-Excitation Wolf-Parkinson-White (WPW) or Mobitz Type II AV Block*; **Urgent**.)
- Atrial fibrillation (see *Figure 13.14 - Atrial Fibrillation*) or flutter (new onset); note the ECG video only mentions atrial fibrillation. (**Urgent**.)
- Third degree AV block or complete A-V block. (see *Figure 13.16 - 3° AV Block*; **Urgent**.)
- An ECG pattern that indicates acute injury or ischemia. (**Immediate**.)

Note: The ECG video states that LBBB is an alert. This is not true for WHI.

In the case of any of these alert statements, the CC physician will decide if it is a true alert and confirm if any further action is required.

- Immediate referrals require immediate notification of the participant during the CC visit and immediate notification of the participant physician via telephone by the CC physician, nurse practitioner, or physician assistant before the participant leaves the CC. Also a follow-up letter documenting the information discussed by phone should be sent as soon as possible.
- Urgent referrals require notification of the participant before she leaves the CC or immediately upon receipt of the finding from the ECG Center and urgent notification of the participant's physician within the week.
- It is not advisable to alarm the participant by revealing these unconfirmed interpretative statements. However, it is helpful to casually inquire if the person has recently had chest pain or discomfort. If the

answer is yes, it is particularly important that you notify a CC physician. A negative answer does not mean that you can ignore the alert; heart attacks are often asymptomatic (silent).

Figure 13.14
Atrial Fibrillation

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Figure 13.15
Sinus Bradycardia

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Figure 13.16
3° AV Block

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Figure 13.17
Sinus Tachycardia $\geq$ 130 bpm

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Figure 13.18
Sinus Tachycardia $\geq$ 140 bpm

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Figure 13.19
Ventricular Pre-Excitation Wolf-Parkinson-White (WPW) or Mobitz Type II AV Block

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13.4 Transmitting ECGs

You may store up to 12 records in your MACPC. Once you have 12 ECGs stored, transmit them to EIPCARE. The MACPC continues to process ECGs when its memory is full but will not store them. You may transmit as many times a day as necessary.
Before transmitting the ECGs to EPICARE,

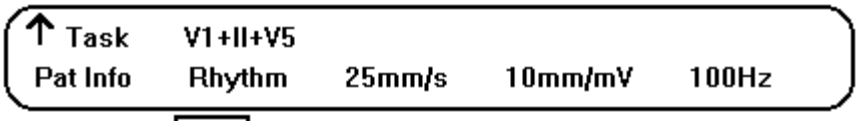
- print the directory (see *Section 13.4.1 – Directory*)
- delete any duplicate ECGs (see *Section 13.4.2.1 – Routine Deletion*)
- verify the participant ID numbers and make any needed corrections (see *Section 13.4.2.2 – Editing an ECG*)

13.4.1 Directory

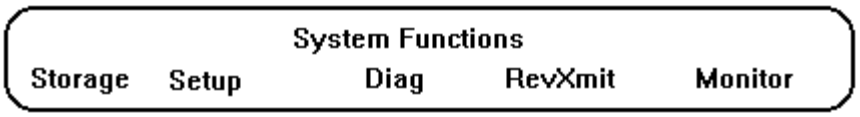
(See Chapter 8 - Directory, MACPC Operator's Manual.)

The directory (**Dirctry**) function allows you to look at what ECGs are stored in the MACPC's memory. This function gives you information such as the participant acrostic and ID number, date when the ECG was taken, how many ECGs are stored in memory, how much of memory is left to store ECGs, etc.
To print a directory, follow these steps below:

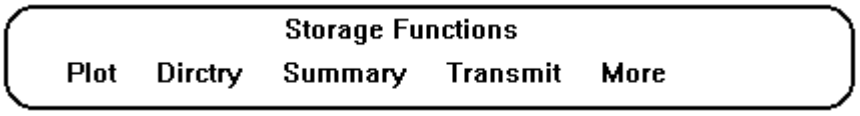
1. If the *Main Menu* is not displayed, press  to return to it:



2. Press  and  at the same time to display the **System Functions** menu. Then press one of the two keys listed under each of the following displays:



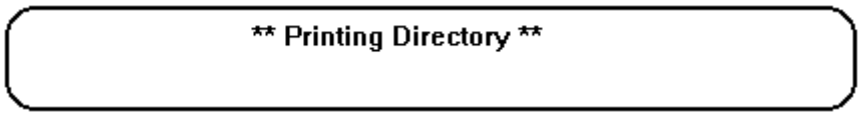
Storage



Directory

3.

4. Selecting **Dirctry** (F2) causes this message to be temporarily displayed:



A directory similar to the following one will be printed:

MACPC-Storage Directory 01-JAN-87-12:37

ID	Name	Date	Time	Type	U/C	Cart	Loc	Site	Room	Size
276778100	GLEN, BRADLEY	01-JAN-87	12:06	ECG	U	001	02	001	806	5%
123456789	WALABIZINSKI, STACHIO	01-JAN-87	12:13	ECG	U	001	01	001	234	4%
332987702	CRUCIAN, ROSE	01-JAN-87	12:22	ECG	C	001	00	001	23	3%

3 ECG(S) 12% Used 88% Free

Compare this to your handwritten log to assure correct information before transmission.

You **MUST** print a directory before transmission so you can delete ECGs which you recorded more than once. Print a final directory after deletions and corrections and attach this to your daily log.

13.4.2 Deleting an ECG and Editing an Invalid ID Number

See Chapter 9 - Deleting an ECG, MACPC Operator's Manual.

13.4.2.1 Routine Deletion

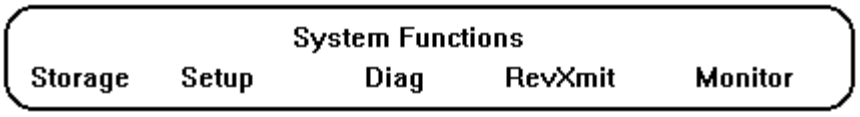
ECGs are usually deleted after you print a paper copy of the ECG, if it is a duplicate record, or when the ECG has been transmitted to the ECG center. When deleting a duplicate ECG, check that you are in fact deleting the correct ECG. The recording time is a good clue.

To delete one or more ECGs, follow these steps:

1. If the Main Menu is not already displayed, press  :

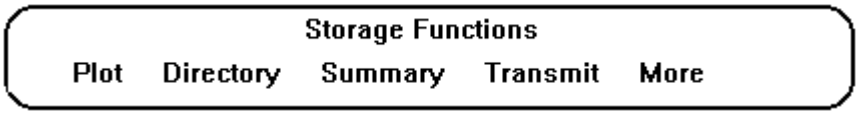
2. Press  and 

at the same time to display the **System Functions** menu.



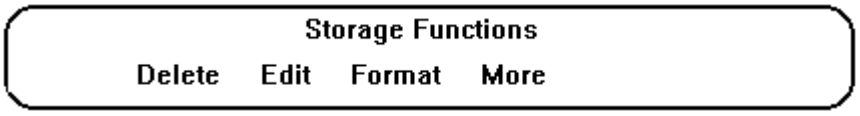
Storage

3.

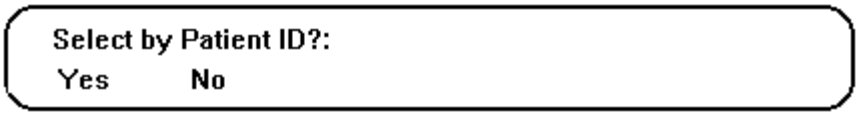


More

4.

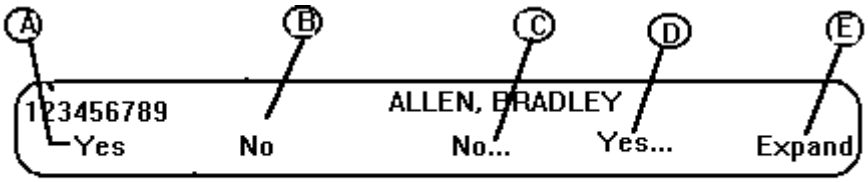


Delete

5. 

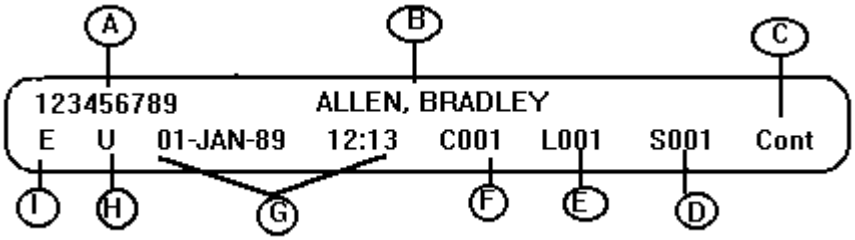
No

6. After selecting **Delete** (F4) a message similar to the following one will be displayed:



A	*Yes*	selects this ECG.
B	*No*	bypasses this ECG.
C	*No...*	bypasses this ECG and all subsequent ECGs.
D	*Yes...*	selects this ECG and all subsequent ECGs.
E	*Expand*	provides additional patient information such as date and time of the ECG. (See step 6.)

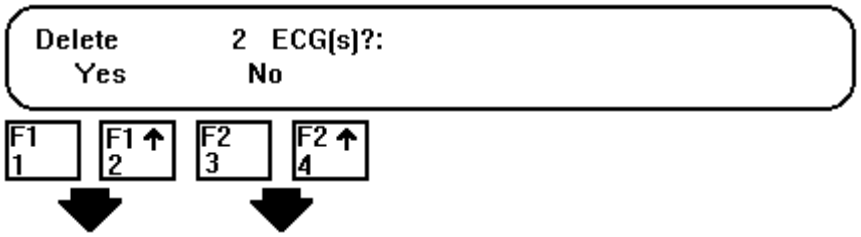
7. To display additional participant information, press **Expand** (F5) and a message similar to the one below will be displayed:



A	Patient identification number	
B	Patient name	Last name, first name of patient or the date and time when ECG was recorded.
C	Cont	Select to return to former display.
D	Site	MUSE* site number where ECG was recorded. (This is 50 for WHI.)
E	Location	Location number (baseline vs. follow-up).
F	Cart number	CC number of unit where ECG was recorded.
G		Date and time when ECG was recorded.
H		U = unconfirmed ECG C = confirmed ECG (use edit function described in Chapter 6 of MACPC Manual to change an unconfirmed to a confirmed ECG).
I	Type of data	E = ECG

*MUSE Marquette Universal System for Electrocardiography.

After you have decided which ECGs you want to delete, you have another chance to change your mind. For example, if you have decided to delete two ECGs, this message would be displayed:



Deletes the selected ECG(s).

Cancels the delete.

Double check the cases you wish to delete especially before transmission.

13.4.2.2 Editing an ECG Report

(See Chapter 6 – Editing ECG Reports, MACPC Operator's Manual.)

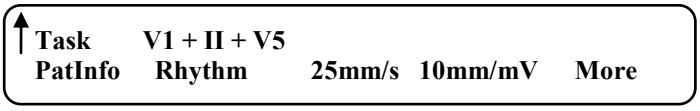
Before transmitting the ECGs to EPICARE, verify the ID numbers in the directory to ensure they are correct and there has not been a key-entry error. Also ensure that the check digit is in the first name field and the acrostic is in the last name field.

Enter:

To edit one or more ID numbers:

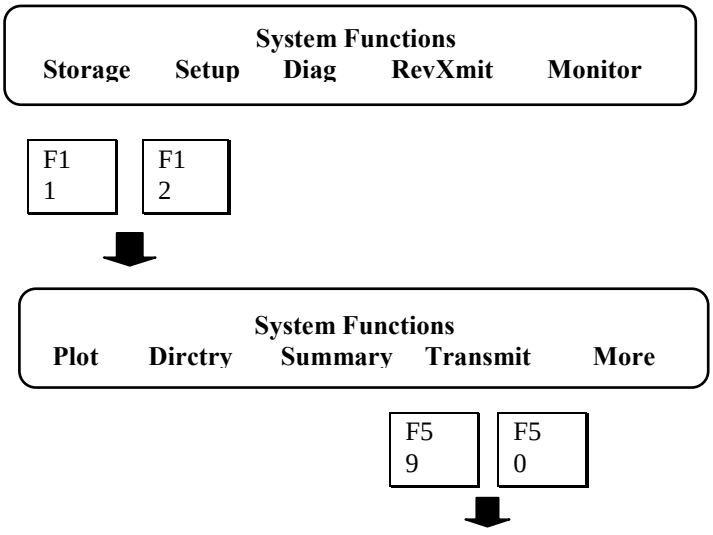
Press Shift F1

1. Display the Main Menu.



2. Display *System Functions* menu. Then press one of the two keys shown under each of the following displays:

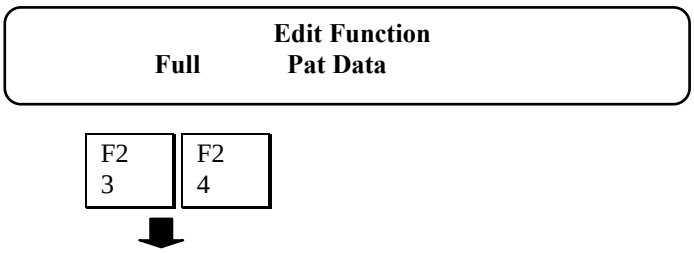
Storage



More

Edit

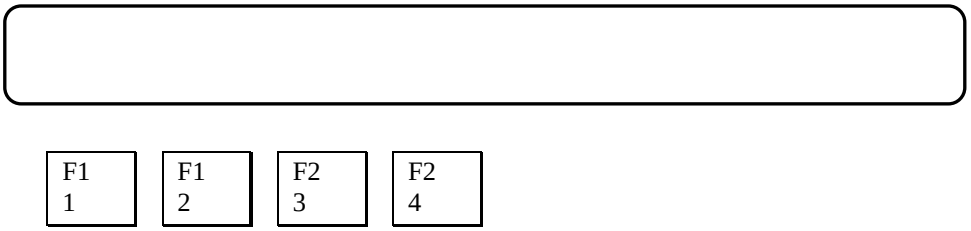
Enter:



PatData

3. Selecting *PatData* (**F2**) displays the following message:

Yes



Continue to press Enter until you reach the invalid ID you want to correct.

4. Press the ENTER Key and a display similar to the following will appear:

You may now edit the ECGs one at a time until the last message is displayed:

↑OK	Stops editing process and changes an unconfirmed report to a confirmed report.	Press Shift F1
↑Kill	Deletes most recent edits and restores information to what it was before the editing process began.	Press Shift F2
↑Print	Prints a preliminary copy of the ECG report you are editing.	Press Shift F3

13.4.3 Transmitting an ECG

Transmit records at the end of each day. To transmit, follow the instructions described below:

1. Send to the ECG Center using the transmitting number 1-910-716-0837. See *Section 0 - 13.1.2.4 Phone* Set-Up.
2. The ECG Center will eMAIL confirmation to you.
3. To confirm all ECGs you sent were received call 1-910-716-0840 for verification. This is not mandatory.
4. Those records with invalid participant ID numbers will be flagged.
5. eMAIL the correct participant ID to the ECG Center. Do not retransmit the record.
6. Proceed to delete the ECGs which were successfully transmitted.
7. The ECG Center's internet address is: EPICARE@PHS.BGSM.WFU.EDU. (No spaces)

13.4.4 Procedures at the End of Each Working Day

- Charge the ECG machine by connecting the power module to the main terminal on the side. This power module must be left plugged in all night and over the weekend when the machine is not in use.
- At the end of the day, the technician should take inventory of the equipment used for the ECG procedures. Any pieces of equipment that are missing should be reported to your supervisor.
- Regularly check and restock needed supplies.

13.5 ECG Quality Assurance Procedures

The ECG quality assurance will follow the well established procedures implemented by the ECG Center for large clinical trials. The implementation of computerized and semi-automated procedures for quality assurance has substantially economized the human effort in visual verification of computer coding.

13.5.1 ECG Quality Assurance at the Clinical Centers

CC Lead Practitioners will all participate in centralized (regional) training sessions in ECG acquisition procedures. Each Lead Practitioner and ECG technician will be individually certified. The certification will require the recording of five consecutive high quality ECGs (Grades 1 or 2).
Quality grades will be coded automatically for all ECGs transmitted. The quality grade is assigned lead by lead on the basis of random noise and worst beat-to-beat drift. Monthly summary reports will be compiled and forwarded to the CCC. Paper ECGs are not acceptable for coding due to lost data points in visual measurement analysis.

The ECG Center will also notify the CCC of all possible combinations of ECG lead reversals that still take place with unexpected frequency. A report specific to each CC will be sent monthly with requests to re-record when necessary or when the possibility of lead reversal is not certain enough to justify automatic correction by ECG software.

13.5.2 Certification in ECG Procedures

The ECG Center will assume the responsibility for Lead Practitioner and ECG technician training and certification. The ECGs recorded by the trainees are transmitted to the ECG Center and graded for quality on the basis of baseline drift and random noise. Each technician has a WHI staff ID coded with the transmitted ECG. Certification requires a successful acquisition and transmission of five successive high quality (Grade 1 or 2) recordings to the ECG Center.

Please note that certification and test ECGs that are transmitted must be clearly marked so as to distinguish them from the actual ECGs transmitted from participants in the study. **For certification and TEST ECGs, use an ID of 9999999** (seven 9s). In the "Referred By" field of the MACPC use the word CERT or TEST. Do not forget to enter the technician's name in the name field and her or his staff ID in the Room No. Field. The ECG Center can then distinguish test and certification ECGs from ECGs on participants. If the recording is to be used for study purposes, it should be retransmitted with the appropriate ID numbers. All Lead Practitioners will receive standardized training from the ECG Center staff and will then train ECG technicians at the CCs, if appropriate. Both Lead Practitioners and ECG technicians must receive certification from the ECG Center.

Each CC should have a copy of the video, "Procedures for Recording an Electrocardiogram," supplied by the ECG Center, and a training video for the MACPC, supplied by Marquette. Review these videos before to recording your first ECG.

13.5.3 Quality Assurance Summary

All CCs **MUST** adhere to the following rules:

- Store only ≤ 12 ECGs. If at the end of the day ≤ 12 ECGs were recorded, transmit them to the ECG Center (daily). If you have need, you may transmit to the ECG Center more than once a day.
- Print directory
- Delete any duplicate ECGs
- Edit incorrect participant IDs (See Chapter 6 - Editing ECG Reports, MACPC Operator's Manual)
- Transmit to the ECG Center
- Print Directory - file

- Edit invalid flagged participant IDs and eMAIL corrections to the ECG Center
- Print final directory - file
- Delete all ECGs from MACPC (Chapter 9 - Deleting an ECG, MACPC Operator's Manual)

Note: All these steps take up to 5 minutes to complete at the end of each day.

Tables 13.2 – Checklist for Recording ECGs and *13.3 – Checklist for ECG Processing* are provided to help remind staff of key points. Post copies of these tables near the MACPC as a reminder.

At least once each month, completely drain and then fully charge the MAC PC's battery. Performing this battery maintenance procedure on a routine monthly basis is strongly recommended to extend battery life and ensure the validity of the LCD "fuel gauge." The procedures for draining and charging batteries can be found on the MAC PC Battery Maintenance document provided to clinics by EPICARE.

Table 13.2

	CHECKLIST FOR RECORDING ECGS	✓ Done?
1	Review WHI Manual of Operations, Vol. 2, Sec. 13.	
2.	Make sure the bed is wide enough to support the participant, especially the left elbow, to help prevent muscle tremors.	
3.	Make sure the participant is comfortable and relaxed, to help prevent muscle tremors.	
4.	Use a blanket to cover the participant if she is cold, to help prevent muscle tremors.	
5.	Make sure the skin is properly prepared. If the skin is oily or scaly, rub vigorously to assure good contact.	
6.	Position the electrodes properly and accurately. Always attach electrodes in the same order. (See Vol. 2, Sec. 13.2.2 – Locating Chest Electrodes and Sec. 13.2.4 – Attachment of Electrode Cables.)	
7.	Make sure there is little or no tension on the connecting wires. (Use narrow strips of Velcro around limb leads to help keep wires in place.)	
8.	Ask the participant to remain relaxed and quiet while you are recording.	
9.	Review the recording for drift, muscle tremor, switching left and right leg leads (tracing shows flat line), or other artifact while the participant is still connected to the machine (see *Vol. 2, Sec. 13.3.2 – Quality Check After Recording*). Make corrections and re-record.	

Table 13.3
CHECKLIST FOR PROCESSING ECGS

			✓ DONE?
1.	Review *Vol. 2, Sec. 13 – ECG Procedures* for correct ECG data entry and lead placement techniques.		
2.	Record participant information on ECG log (*Form 91*) as each ECG is performed.		
3.	Enter participant data in the correct MACPC fields.		
	MACPC FIELD	**PARTICIPANT DATA**	
	• New Patient	Enter Yes/No.	
	• Patient's Last Name	Enter first 4 letters of last name only.	
	• Patient's First Name	Enter the last digit (letter) of the participant's ID number.	
	• Patient's Identification Number	Enter first 7 digits of the participant's ID number.	
	• Location Number	Enter baseline or follow-up sequence number For: Enter: Screening visit AV3 AV6 AV9 Closeout	
	• Room Number	Enter WHI staff ID number.	
	• Patient greater than one year of age	Enter Yes.	
	• Age	Enter participant's age in years.	
	• Height	Enter E measurement.	
	• Weight	Enter V6 measurement.	
	• Sex	Enter female.	
	• Race	Press enter.	
	• Medications	Press enter.	
4.	Print a directory (see Vol. 2, *Sec. 13.4.1 – Directory* or MACPC operator's manual, Chapter 8 – Directory) and check it against your log entries before you transmit. • Edit any invalid ID numbers (see *Vol. 2, Sec. 13.4. – Transmitting ECGs* or MACPC operator's manual Chapter 6 – Editing ECG Reports), and • delete any duplicate records before transmission. If you transmit duplicate records, contact Epicare the same day to delete the duplicate. It is very important that this is done the same day.		
5.	Transmit on a regular schedule, or before you have 12 records stored in your MACPC.		
6.	Delete the transmitted records after receiving e-mail confirmation of receipt from Epicare (see *Vol. 2, Sec. 13.4.3 – Transmitting an ECG* or MACPC operator's manual, Chapter 9 – Deleting an ECG). If you can't wait for e-mail confirmation, call Epicare directly. DO NOT re-transmit the same records unless directed to by Epicare.		

Section 13
ECG Procedures

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SECTION 15

MEDICATIONS (STUDY PILLS)

INTRODUCTION

Clinical Center (CC) staff members dispense study pills to participants in Hormone Replacement Therapy (HRT) and Calcium and Vitamin D (CaD) components of the Clinical Trial (CT) and provide instructions on how to take the daily study pills.

McKesson BioServices Corporation (McKesson) receives the HRT and CaD pills from the drug manufacturers, inventories, stores and labels the bottles with unique bottle numbers, and ships the labeled bottles to the CCs. Enrollment pills for HRT are packaged in bottles of 50 pills. Study pills for the treatment arms after randomization are packaged in bottles of 215 pills, and open label hormones in bottles of 100. Calcium and Vitamin D study pills are packaged in bottles of 215 chewable tablets and 430 swallowable pills.

The CCs store a 1- to 2-month supply of HRT and CaD bottles, use WHILMA to select the appropriate bottles to dispense to each participant, label the bottles with the participant's name and ID number, dispense the bottles to the participant at regularly scheduled appointments or as needed, record receipt of returned bottles, and assess the participant's study pill adherence.

This section gives a description of the medication storage facility at each CC; the procedures for receiving, selecting, labeling, and dispensing the medications to participants; the procedures for assessing the participant's adherence to taking the study medications; the procedure for shipping returned study pill bottles to McKesson; and procedures for reporting serious adverse experiences.

15.1 Medications (Study Pills)

15.1.1 HRT Component

Wyeth-Ayerst (W-A) supplies all the HRT enrollment and study pills for the Women's Health Initiative (WHI).

15.1.1.1 Enrollment Pills

The drug manufacturer provides enrollment pills in bottles of 50 pills.

McKesson labels and ships HRT enrollment bottles to CCs in boxes labeled "HRT ENROLLMENT." Each box contains 36 bottles.

15.1.1.2 HRT for Randomized Participants

The following four types of HRT study pills are provided:

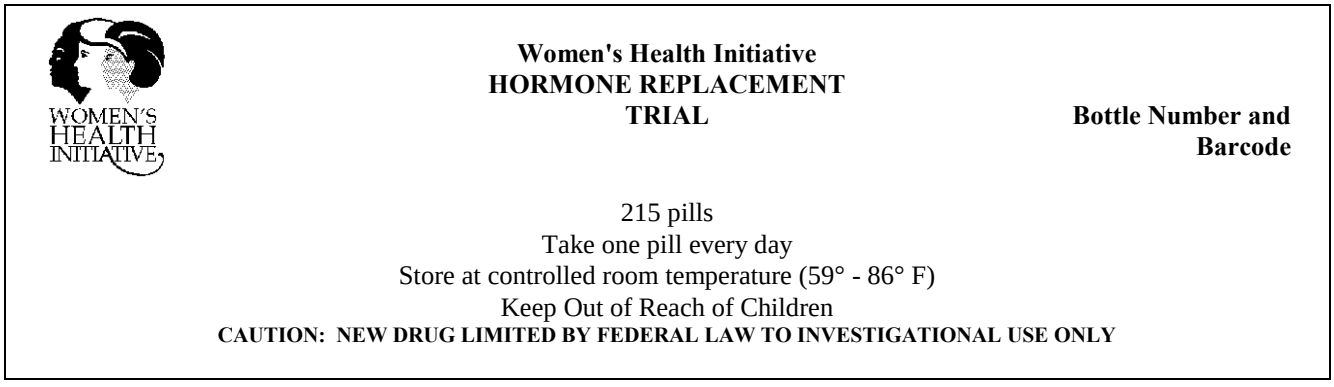
- ERT pills: conjugated equine estrogen (CEE) 0.625 mg
- ERT placebo pills: conjugated equine estrogen (CEE) placebo
- PERT pills: conjugated equine estrogen (CEE) 0.625 mg plus medroxyprogesterone (MPA) 2.5 mg
- PERT placebo pills: conjugated equine estrogen (CEE) plus medroxyprogesterone (MPA) placebo

See *Tables 15.3 - WHI Placebo Ingredients (PERT Placebo)* and *15.4 - WHI Placebo Ingredients (ERT Placebo)* for listings of HRT placebo study pill contents.

The HRT study pills (ERT, PERT and their corresponding placebos) are supplied in bottles of 215 pills. McKesson labels each bottle with the sample label shown in *Figure 15.1 - Sample HRT Label.*

McKesson ships the labeled HRT study pill bottles to CCs in boxes labeled "HRT" and either "hysterectomy" or "no hysterectomy." Each box contains 60 bottles with a specified proportion of ERT and ERT placebo in the "hysterectomy" box and PERT and PERT placebo in the "no hysterectomy" box.

Figure 0-1
Sample HRT Label



15.1.1.3 Open Label Study Pills

Open label hormones are supplied in commercially-labeled bottles of 100 pills. The commercial labels contain the hormone name and dose. McKesson ships these bottles to the CCs in boxes labeled "HRT Open Label" and the corresponding type of study pills. Each box contains 5 bottles.

The following types of open label hormones are supplied:

- conjugated equine estrogen (CEE) 0.3 mg
- conjugated equine estrogen (CEE) 0.625 mg
- medroxyprogesterone (MPA) 2.5 mg
- medroxyprogesterone (MPA) 5 mg
- medroxyprogesterone (MPA) 10 mg

15.1.2 CaD Component

The drug manufacturer provides the following two types of CaD study pills:

Mint-flavored chewable tablets

- Calcium carbonate containing 500 mg elemental calcium plus vitamin D_3 200 IU or placebo
- Each bottle contains 215 CaD study pills
- Each box contains 24 bottles

In addition to the regular cartons of chewable CaD study pills, a second configuration type called "BCaD" is available. The purpose of the BCaD is to prevent an individual clinical center's chewable CaD inventory from becoming "out of balance." Inventory is considered out of balance when a clinic has several partially-used cartons open but is unable to dispense from any of them.

BCaD cartons contain 24 bottles of chewable CaD. Each bottle contains 215 CaD study pills. The study pills in the BCaD cartons are identical to those in the regular CaD bottles. Procedures described elsewhere in this section for the dispensation, adherence collection and disposal of chewable CaD pills also apply to pills taken from BCaD cartons.

Swallowable pills

- Calcium carbonate containing 500 mg elemental calcium plus vitamin D_3 200 IU or placebo (reformulated from 125 IU to 200 IU Vitamin D in Spring 1998)
- Each bottle contains 430 CaD study pills
- Each box contains 48 bottles

See Table 15.6 – WHI Placebo Ingredients (CaD Placebo) for a listing of CaD placebo ingredients.

McKesson labels each bottle with the sample CaD label shown in *Figure 15.2 - Sample CaD Labels (a. Chewable Tablets, b. Swallowable Pills)*. McKesson ships supplies of CaD to CCs. Each box of CaD study pills has a specified proportion of active and placebo study pills.

Figure 15.2
Sample CaD Labels
a. Chewable CaD Tablets

Women's Health Initiative
CALCIUM/VITAMIN D TRIAL

Bottle Number and Barcode

215 Tablets
Chew One Tablet 2 Times a Day with Food
Store at Controlled Room Temperature (59° - 86° F)
Pkg/Dist: McKesson BioServices, Rockville, MD 20850
Keep Out of Reach of Children
CAUTION: NEW DRUG LIMITED BY FEDERAL USA LAW TO INVESTIGATIONAL USE

b. Swallowable CaD Pills

Women's Health Initiative
CALCIUM/VITAMIN D TRIAL

Bottle Number and Barcode

430 pills
Do not chew
Take One Tablet 2 Times a Day with Food. "Do Not Chew"
Store at Controlled Room Temperature (59° - 86° F)
Pkg/Dist: McKesson BioServices, Rockville, MD 20850
Keep Out of Reach of Children
CAUTION: NEW DRUG LIMITED BY FEDERAL (USA) LAW TO INVESTIGATIONAL USE

15.1.3 Child-Resistant Caps (Required)

Routinely offer participants a non-child resistant cap each time study pills are dispensed. All HRT and CaD bottles come with child-resistant caps. Embedded within each of these caps is a non-child resistant cap. Follow the procedures below if a participant requests a non-child-resistant cap.

- Ask the participant to sign and date a statement requesting a non-child-resistant cap. A participant needs to complete this form one time, not each time you give her a new bottle (see *Figure E.5.9 - Model Statement for Non-Child-Resistant Cap* for a sample statement).
- Remove the child-resistant cap from the bottle before dispensing and replace it with a non-child-resistant cap.
- File the signed statement in her participant file.

Removing the Child-Resistant Portion of a Study Pill Cap

Use the following directions to remove the child-resistant portion of the full cap assembly:

1. Take the cap off a bottle to see the two parts. The outer cap is made of white plastic (the part you had to push down while turning to remove the cap). Inside that cap is what looks like a liner, made of a less opaque white plastic.
2. Screw the cap back on the bottle.

3. The outer white plastic cap can be flipped off easily, using a strategy similar to opening a soda bottle with a bottle opener. Use a cap remover (purchased from a pharmaceutical supply house) or wedge the white safety cap into the handle of a file drawer or door, push down on the bottle itself, and the white top should pop off.
4. The portion of the cap that remains on the bottle (non-child-resistant portion) can be twisted on and off in the usual manner.
5. If you want to replace the child-resistant portion of the cap, just place it over the portion remaining on the bottle and push down firmly--it helps to get your weight on it!
6. CAUTION: Do not use a hand tool, such as a screwdriver, to try to pry the top off. The child-resistant portion of the cap is meant to be popped off, not pried off. Clinical Centers may want to purchase specialized tools for this purpose.

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15.2 Study Pill Storage Area (Required)

Each CC is responsible for maintaining a secure area for storing both HRT and CaD study pills. This storage area could be a small room with shelves and counter space or a larger multi-purpose room with locking cabinets for the boxes and nearby working counters or tables.

15.2.1 Storage Area Specifications

Each CC should have a secure storage area. This room should not be open to the public. The storage room should be locked when not in use. The area should be adequate to contain the following:

- A 2-month supply of all HRT and CaD study pills. Each HRT enrollment and open-label study pill box is 12" wide x 12" deep x 4.5" high. HRT randomized study pill boxes are 12" wide by 20" deep x 4" high. Chewable CaD study pill boxes are 23" long x 16" wide x 8" tall and swallowable CaD study pill boxes 19 3/8"wide x 12 7/8" deep x 6 1/2" high (approximately). See *Section 15.3.1 - Minimum Inventory (Required)* for minimum number of each type of study pills to store.
- Scale for weighing bottles and study pills.
- Adequate counter space for all activities related to study pill handling.

15.2.2 Storage Area Organization

It is helpful to keep each distinct study pill type in separate areas within the storage room. The room can be separated in the following distinct areas:

HRT: Enrollment pill bottles
Randomized study pill bottles for "hysterectomy"
Randomized study pill bottles for "no hysterectomy"
Open label hormone bottles:
CEE 0.3 mg
CEE 0.625 mg
MPA 2.5 mg
MPA 5 mg
MPA 10 mg
Returned or discarded HRT study pills

CaD: Randomized chewable study pill bottles, including bottles from BCaD cartons
Randomized swallowable study pill bottles
Returned or discarded CaD study pills

15.2.3 Storage Area Work Space

The storage area should be equipped with a work space to:

- Unpack study pill shipments from McKesson and process corresponding paperwork.
- Accommodate one PC connected to CC's LAN (or have one close by).
- Select study pill bottles during participant's visit or contact and enter dispensing and adherence information in the database.
- Weigh study pills/bottles for adherence.
- Package and mail study pill bottles to participants when necessary.
- Package and ship returned, expired, damaged or other unusable bottles to McKesson, as appropriate.
- Maintain records of study pill shipments sent and received.

15.3 Study Pill Inventory Maintenance

15.3.1 Minimum Inventory (Required)

Clinical Centers should maintain a 1- to 2-month supply of all HRT and CaD study pills. The minimum supply level for each is:

Type		Minimum
HRT	Enrollment pill boxes	1 box of 36 bottles
	Randomized HRT boxes:	
	hysterectomy	1 box of 60 bottles
	no hysterectomy	1 box of 60 bottles
	Open label hormone boxes:	
	conjugated equine estrogen (CEE) 0.3 mg	1 box of 5 bottles
	conjugated equine estrogen (CEE) 0.625 mg	1 box of 5 bottles
	medroxyprogesterone (MPA) 2.5 mg	1 box of 5 bottles
	medroxyprogesterone (MPA) 5 mg	1 box of 5 bottles
	medroxyprogesterone (MPA) 10 mg	1 box of 5 bottles
CaD	Randomized CaD boxes	
	chewable study pills	1-3 boxes of 24 bottles
	BCaD chewable study pills	2 boxes of 24 bottles
	swallowable study pills	1-2 boxes of 48 bottles

Determine the study pill supply needed based on your CC's randomization rates and follow-up contact schedule.

Note that you may need to open a new box of study pills before dispensing all the bottles in a box that is currently open. Monitor your study pill supply and order more boxes from McKesson before you complete one box. For CaD you also need to allow for the approximate 2-week delivery time.

Note that maintaining BCaD inventory requires an additional step: when <u>any</u> BCaD carton in inventory drops to eight bottles or less, contact McKesson and order a new BCaD carton to replace it. Do this even if you have other BCaD cartons with more than eight bottles. In your order to McKesson, reference the 6-digit carton ID number of the BCaD carton that you are replacing. McKesson can't fill BCaD orders without this carton ID number.

Run a *Drug Inventory Report* (*WHIP 0032*) from WHILMA on a regular basis (at least quarterly) and resolve any discrepancies between the report and your actual inventory. (See *Table 15.1 - List of Discrepancies Between Drug Inventory Report and Actual Inventory, Possible Causes, and Actions to Take).*

15.3.2 Request Study Pills from McKesson (Required)

McKesson ships study pill bottles to CCs in response to orders placed by the CCs. Each CC is responsible for updating its projections and maintaining adequate supplies based on a projected 1- to 2-month period.

To request additional study pills from McKesson:

- Estimate the CC's study pill needs for the next 1- to 2-month period.
- Send the request to McKesson via DaVinci eMAIL (use phone or fax if eMAIL is not convenient). (See the WHI Directory for phone numbers and addresses.)
- Telephone emergency requests to McKesson and follow up with an eMAIL message or fax
- If ordering BCaD from McKesson, reference the carton ID number of the carton you are replacing as described in *Section 15.3.1 – Minimum Inventory.*

Table 15.1
List of Discrepancies Between Drug Inventory Report (WHIP 0032) and Actual Inventory, Possible Causes, and Actions to Take

Discrepancy	Possible Cause	Action
According to the report, a bottle is neither dispensed nor disabled, but is missing from inventory.	1. Bottle was given to a participant without using WHILMA to select the bottle number (e.g., selection of enrollment bottle was not recorded on backup form or has not yet been key-entered). 2. Bottle selection was made using WHILMA but transaction was not committed by pressing F10 in WHILMA. 3. Staff person key-entered the bottle number (instead of scanning the barcode on the bottle label) and made an error in the key-entry. 4. Bottle was discarded due to damage or loss but was never disabled in WHILMA. 5. Barcode label on bottle was incorrect or bottle was in incorrect position in box.	Make a note of the dispensation dates of other recently-dispensed bottles from that carton. Using the randomization log, clinic appointment schedule, and contact notes from participant files, try to determine which participant received the missing bottle. Confirm the bottle number with the participant before contacting the CCC Data Coordinator to make any changes in WHILMA. If you determine that the bottle was discarded due to damage or was lost before it could be dispensed, enter the date discarded as the "disable date" in the Medication Inventory Management screen of WHILMA.
A bottle listed as dispensed on report is still in inventory.	1. Staff person selecting bottle key-entered the bottle number instead of scanning the barcode on the bottle label and made an error in key-entry.	Review file of participant to whom bottle was supposedly dispensed. Contact participant if necessary to verify the correct number of the bottle dispensed. Contact CCC Data Coordinator to correct the data in WHILMA.

15.3.3 Receiving Study Pills (Required)

Each CC should designate a staff member to be responsible for unpacking and storing the pills. Upon receiving a shipment from McKesson:

- Verify the contents of the carton with the enclosed packing slip.
- Send an email message to McKesson acknowledging receipt of the shipment.
- Record receipt of boxes in WHILMA following data management instructions (see *Vol. 5 – Data System, Section 7.3.3.1 – Conducting Study Medication Inventory*).
- Store the boxes in the designated location in the medications storage area with the labels showing.

15.3.4 Returning Study Pills to McKesson (Required)

15.3.4.1 Returning HRT Study Pills

Ship all HRT study pills returned by participants to McKesson for disposal. At times, McKesson will also request return of unused or expired pills. McKesson has assumed the responsibility for proper disposal of the unused pills as required by the Investigational New Drug (IND) requirements. The pills are toxic in high doses and are thus considered "hazardous waste."

Return only the pills; discard the empty bottles (after blacking out the participant's name on the label).

1. Label an empty study pill carton or other cardboard box with "Return Study Pills." Place a heavy-duty plastic bag (must be 1.0 mil thickness or greater) or plastic container in the box. Do not use plastic bags that are sealed with a zip lock mechanism.
2. Place the box on a counter in a secure location.
3. After weighing returned pills [see *Section 15.6.2.2 – Medications (Study Pills)*], place the pills in the plastic bag (do not mix HRT with the two forms of CaD pills). Do not fill the bag with more than 25 pounds of discarded pills.
4. When the bag is no more than three quarters full or 25 pounds in weight (whichever comes first), fold the top of the bag down twice and seal with heavy-duty tape such as mailing tape or duct tape. Do not use masking tape or cellophane tape for this purpose.
5. Put the sealed bag into another heavy plastic bag and seal the second bag with heavy-duty tape.
6. Write "discarded HRT" on a self-adhesive label and place the label securely on the outer bag.
7. Pack the bag into a heavy-duty corrugated cardboard container. It is acceptable to use a used cardboard carton for this purpose if the carton is in good condition. Do not use a carton that shows signs of wear or weakness from previous use.
8. Weigh the packed carton to make sure that it does not exceed 25 pounds.
9. Use heavy-duty tape and seal the carton well so that it will not break open during shipment. Label the carton with a pre-printed McKesson address label.
10. Mark the CC name and return address clearly on the outside of the carton.
11. Ship the cartons of returned pills to McKesson. Use the least expensive method (e.g., regular mail or UPS) to ship the cartons.
12. McKesson will ensure proper disposal of the pills.

15.3.4.2 Returning CaD Study Pills

Clinical Centers should dispose of CaD study pills appropriately. You can return study pills to McKesson or dispose of returned CaD study pills at your CC following the state and institutional regulations to ensure safety. In addition, each CC disposing of CaD study pills must account for the number of each type of study pills discarded. This is required by the Investigational New Drug (IND) agreement.

1. Determine and document your state, local and/or institutional requirements for disposal of CaD study pills. Develop a log to track chewable and swallowable CaD study pill disposal separately. An example of a CaD disposal log is given in *Figure 15.3 – CaD Disposal Log Example*.

   If a CC does not have the resources to provide for safe and legal disposal, or chooses to continue to mail the returned CaD study pills back to McKesson, do so via surface or other low cost mailing system. Follow the instructions in *Section 15.3.4.3 – Returning Discarded CaD Pills to McKesson* when preparing the pills for shipment.

2. CaD "chewable" and "swallowable" study pills must be accounted for separately. Use the following procedures to account for and dispose of CaD study pills:
   - Label one box "Chewables" and the second "Swallowables." Also record an "identifier" on each box (example: #1 Chewables).
   - Place a heavy-duty plastic bag(1.0 mil thickness or greater) or plastic container in each of the boxes. Do not use plastic bags that are sealed with a zip lock mechanism.
   - Weigh each of the boxes and record the weights on your logs (columns A and B).
   - Assess adherence on CaD study pill bottles as directed in *Vol. 2, Section 15.6.2.2 – Bottle Weighing Procedure.*
   - Place CaD chewable tablets and swallowable pills in the plastic bags lining the appropriate disposal boxes as described in *Section 15.3.4.1 – HRT Study Pills.*
   - When a disposal box full, weigh the box. Record this weight in your log (column C).
   - Calculate the weight of the pills by subtracting column B from column C. Record this value in your log (column D).
   - Calculate the estimated number of pills you are disposing by multiplying the value in column D by 338. (1 kg chewables = 338 tablets, 1 kg swallowables = 791 pills). Record the number of pills or tablets on your log (column E).
   - Record the date the disposal box is removed from your CC (column F).

3. Archive the CaD Disposal Logs for future reference (see *Figure 15.3 – CaD Disposal Log Example*).

15.3.4.3 Returning Discarded CaD Pills to McKesson

If you choose to return the pills to McKesson for disposal, follow these steps for preparing the returned pills for shipment:

- When a disposal box is no more than three quarters full or 25 pounds in weight (whichever comes first, remove the plastic liner bag with the pills in it from the box.
- Fold the top of the bag down twice and seal with heavy-duty tape such as mailing tape or duct tape. Do not use masking tape or cellophane tape for this purpose.
- Put the sealed bag into another heavy plastic bag and seal the second bag with heavy duty tape.
- Write "discarded CaD" on a self-adhesive label and place the label on the outer bag.

- Pack the bag into a heavy-duty corrugated cardboard container It's acceptable to use a used cardboard carton for this purpose if the carton is in good condition. Do not use a carton that shows signs of wear or weakness from previous use.
- Weigh the packed carton to confirm that it doesn't exceed 25 pounds.
- Use heavy-duty tape and seal the carton well so that it will not break open during shipment. Label the carton with a pre-printed McKesson address label.
- Mark the CC name and return address clearly on the outside of the carton.
- Ship the cartons with returned pills to McKesson. Use the least expensive method (e.g., regular mail or UPS) to ship the carton.

Figure 15.3
CaD Disposal Log Example

Box (A)	**Empty Box Weight (B)**	**Full Box Weight (C)**	**Weight of Pills (D)** **[C - B]**	**Calculated Number of Pills (E)** **[D x 338] (chewable)** **or** **[D x 791] (swallowable)**	**Date of Disposal (F)**
#1 (chewables)	10 kg	56 kg	46 kg	46 x 338 = 15,548	2/17/97
#2 (swallowable)	10 kg	30 kg	20 kg	20 x 791 = 15,820	3/16/98

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15.4 Study Pill Dispensing (Required)

Dispense study pill bottles to participants at regularly scheduled contacts. You may also dispense study pill bottles through the mail as needed (see *Section 15.5 - Selecting and Dispensing Problems (Required).* All study pill bottles must be selected in WHILMA.

Clinical Centers should be familiar with and follow state and institutional regulations regarding dispensing of medications.

15.4.1 Selecting and Dispensing Enrollment HRT Bottles at Screening Visit 2 (SV2) (Required)

Select and dispense one enrollment pill bottle (or more, if necessary) and supporting materials to each participant interested in HRT at SV2. Supporting materials include a 7-day pill organizer, *Form 53 - HRT Calendar* (if she has a uterus), and an *HRT Handbook*.

15.4.1.1 Preparation (Required)

Ensure that a bottle label is in the participant's file.

- The bottle label has the CC name and phone number, the participant's name, and the participant's ID number with corresponding barcode label. These labels are usually printed after the participant has been assigned a participant ID number and has signed an HRT Consent Form (see *Vol. 5 - Data System, Section 7.3.3.2 - Printing Bottle Labels*).
- Do not attach the label to a bottle at this time.

15.4.1.2 Selecting and Dispensing at SV2 (Required)

After you determine a participant's interest in participating in HRT, select the HRT enrollment bottle as described in *Vol. 5 - Data System - Section 7.3.3.3 - Selecting Run-In (Enrollment) HRT Bottles*.

If desired, print out a *Dispensation Report* (*WHIP 0232)* and file it in the participant's file.

Ask the participant if she prefers a non-child resistant cap, and obtain the proper consent, as appropriate.

Give the bottle to the participant. Remind her to bring the bottle back at the next visit.

> *Note*: Give the enrollment pill bottle to the participant **only after** you have labeled the appropriate bottle with the participant's name and ID number.

Give her the *HRT Handbook* (see *Appendix F - Required CC Participant Materials*), the 7-day pill organizer, and *Form 53 - HRT Calendar* (if she has a uterus). Explain:

- Study pill instructions, using the *HRT Handbook*.
- What she could expect when she takes the pills, using the *HRT Handbook*.
- How to remember to take pills, using the pill organizer.
- How to record any bleeding, using *Form 53 - HRT Calendar* (as appropriate).

See Section 5.2 - Initiating the HRT Intervention at SV2 for further reference.

If screening visit 3 (SV3) is delayed to the point that the participant runs out of enrollment pills, an additional bottle(s) of HRT enrollment pills can be dispensed as part of her initial enrollment period. See *Section 15.5.4 - Participant's Supply Runs Out (Required).*

15.4.1.3 Repeat HRT Enrollment Period

If a participant is ineligible due to poor adherence on her first enrollment period, she may undergo a second enrollment period. Use this second enrollment period option only if she has failed (is ineligible) due to adherence to her first enrollment period and there is a reasonable expectation that she will be adherent this second time. WHILMA will ignore the data from the first enrollment period and use only the data from the second enrollment period to determine the participant's adherence to the HRT enrollment pills.

Use the following steps to start the second enrollment period:

- Select a new bottle of HRT enrollment pills.
- In the selection screen, indicate that this is a repeat enrollment period by recording "2" for run-in attempt number. Only record a "2" if the participant has failed adherence to her first enrollment period.
- Dispense the HRT enrollment pills to the participant as you did for the first enrollment period.
- Assess adherence as you did for the first enrollment period.

15.4.1.4 Selecting Enrollment Pills When There are Computer Problems (Required)

If the PC usually used for dispensing is not working, attempt to use another PC to select and dispense HRT enrollment pills. If WHILMA is down, use the back-up form (*Form 955 - Enrollment Pill Dispensing*) and enter the data into WHILMA later. **Always use the scan gun** to enter the bottle number into WHILMA. Only key-enter the ID numbers in the appropriate fields only if you are unable to scan the barcode labels due to a malfunctioning scan gun. If the scan gun is not working properly, contact the CCC Data Coordinator as soon as possible for repair/replacement.

15.4.2 Selecting and Dispensing HRT Bottles at Screening Visit 3 (SV3) (Required)

Dispense one HRT bottle to each participant you randomize at SV3. Ask those participants whose eligibility determination you cannot complete to continue on enrollment pills. The need to continue enrollment pills can occur, for example, if you have not yet received the lab or mammography results. You may need to select and dispense an additional bottle of HRT enrollment pills.

15.4.2.1 Preparation (Required)

Ensure that a barcode bottle label with the CC name and phone number, participant's name, and the participant's ID number is in her file. Do not attach the label with the participant ID number and name to the bottle at this time.

15.4.2.2 Selecting and Dispensing at SV3 (Required)

- Confirm the eligibility status of the participant at SV3. If you cannot complete the eligibility determination of the participant by SV3, return the HRT enrollment pill bottle to her. Dispense an additional HRT enrollment bottle if necessary.
- If the participant is eligible, randomize her to HRT (see *Vol. 5, Section 6 - Eligibility Determination and Randomization*).
- Select the study pill bottles to dispense to the participant as described in *Vol. 5 - Data System, Section 7.3.3.4 - Selecting Study Medications*.
- You must use WHILMA to select the appropriate HRT study pill bottles for the participant. Do not give a participant a bottle if it has not been selected by WHILMA. Dispense the study pill bottle to the participant only after you have labeled the appropriate bottle with the participant's name and ID number. Do not give the bottle to the participant if there is any question whether the transaction has been accepted in WHILMA.

- Print out a *Dispensation Report (WHIP 0232),* if desired, and file it in the participant's file.
- Give the appropriately-labeled bottle to the participant. Ask her if she prefers a non-child resistant cap. Give her another *Form 53 - HRT Calendar*. Ask her if she needs another *HRT Handbook*. Instruct her on how to take the pills. Remind her to bring the bottle back at the next visit.

15.4.3 Selecting and Dispensing HRT Study Pill Bottles at Semi-Annual and Annual Visits (Required)

HRT study pills may be dispensed at semi-annual contacts or at annual visits. Dispense an annual supply only at annual visits, not at semi-annual visits. Dispensation of HRT study pills should not be made until appropriate safety procedures have been completed. (*See Section 16 - Follow-Up Contacts*). If the participant has had a hysterectomy since the last dispensation, contact the CCC Data Coordinator before dispensing additional HRT study pills (see also *Section 5.5.1 - Management of HRT after Hysterectomy for Non-Cancerous Condition*).

15.4.3.1 Preparation

Before a regularly scheduled semi-annual and annual visit, check to make sure you have bottle labels with the participant ID number and name for the participant's bottle of HRT study pills.

15.4.3.2 Selecting and Dispensing at Follow-up Contacts (Required)

- Select the study pill bottles to dispense to the participant as described in *Vol. 5, Section 7.3.3.4 - Selecting Study Medications*.
- You **must** use WHILMA to select the appropriate HRT study pill bottles for the participant. Do not give a participant a bottle if it has not been selected by WHILMA. Dispense the study pill bottle to the participant **only after** you have labeled the appropriate bottle with the participant's name and ID number. Do **not** give the bottle to the participant if there is any question whether the transaction has been accepted in WHILMA.
- Print out a *Dispensation Report (WHIP 0232)*, if desired, and file it in the participant's file.
- Give the appropriately-labeled bottle to the participant. Ask her if she prefers a non-child resistant cap. Ask her if she needs another *HRT Handbook*. Instruct her on how to take the pills. Remind her to bring the bottle back at the next visit. You may choose to affix a sticker to the bottle reminding the participant to return the bottle at her next clinic visit.

15.4.4 Selecting and Dispensing Open Label HRT Study Pills (Required)

The CC gynecologist may decide that a participant needs open label hormone medications. This decision may be made after scheduled visits or after an unscheduled visit for vaginal bleeding. Most often, open label hormones will be dispensed in response to results obtained from an endometrial aspiration, but they may also be dispensed in response to other treatment side effects (see *Section 5.4 - Managing Symptoms* for more details).

- Complete a *Form 54 - Change of Medications* each time you ask the participant to start, stop, or change the dosage of HRT study pills or open label medications. Record the date of the change, dosage of hormones and length of time prescribed. Algorithms and time frames are described in *Section 5.4 - Managing Symptoms*.
- Select and dispense open-label medication as described in *Vol. 5, Section 7.3.3.4 - Selecting Study Medications*.

- You must use WHILMA to select the appropriate open-label study pill bottle for the participant. Do not give a participant a bottle if it has not been selected by WHILMA. Dispense the open-label study pill bottle only after you have labeled the appropriate bottle with the participant's name and ID number. Do not give the bottle to the participant if there is any question whether the transaction has been accepted in WHILMA.
- Print out a *Dispensation Report* (*WHIP 0232*), if desired, and file it in the participant's file.
- Give the appropriately-labeled bottle to the participant. Ask her if she prefers a non-child resistant cap.
- Instruct the participant on how to take the open-label hormones.

  For example: "*Stop your normal WHI HRT pills. Take one of these pills daily*."
  or: "*Continue your normal WHI HRT pills. Take two of these pills daily*."

- Instruct the participant to bring the bottle back to the CC at her next CC visit (this will often be at unscheduled times for these participants).

15.4.5 Selecting and Dispensing CaD Study Pills (Required)

Calcium and Vitamin D study pills should be dispensed at the time of randomization to CaD using procedures similar to HRT study pill dispensing. See *Section 15.4.2 - Dispensing HRT Bottles at Screening Visit 3 (SV3) (Required).* If the participant is eligible for CaD, randomize her to CaD, determine her preferred formulation, and select the appropriate CaD study pill bottle(s) to dispense as described in *Vol. 5, Section 7.3.3.4 - Selecting Study Medications.* Provide the participant with the *CaD Information Sheet (*see *Appendix - F.2.5 - You're an Important Part of the CaD Program*). Note: You will be dispensing two bottles for the first six-month period if the participant chooses the CaD chewable tablets or one bottle if she chooses the CaD swallowable pill. Dispense only a 6-month supply to the participant to ensure she is tolerant of the formulation. An annual supply may be dispensed once she has taken the same formulation for at least one year. Clinical Centers have the option of mailing the second 6-month supply (rather than conducting a visit), but should carefully assess the need for a participant to come in for a clinic visit.

CaD study pills are also dispensed at semi-annual and annual contacts using procedures similar to HRT study pills. See *Section 15.4.3 - Selecting and Dispensing HRT Study Pill Bottles at Semi-Annual and Annual Visits (Required).* Participants should be offered the *CaD Information Sheet* and given study pill instructions each time CaD pills are dispensed. Note: You will be dispensing two bottles for each six-month period (4 bottles for a year) if the participant chooses the CaD chewable tablets or one bottle for each six-month period (2 bottles for a year) if she chooses the CaD swallowable pill. A 12-month dispensation can be done only at an annual visit contact.

15.4.6 Switching CaD Formulations

CaD formulations can be switched at any time, however, it is always best if you can wait until the next semi-annual (SA) or annual visit (AV) to minimize CC burden and preserve pill inventory. Remember, when a formulation is being switched, you need to collect the participant's old study pill bottle(s) and enter an actual weight or, if you are unable to collect the bottles, enter an estimated count, in WHILMA before dispensing the new formulation. Make every attempt to follow-up with the participant and collect the bottles if you did use an estimated count.

Switching formulations can be handled during an in-person clinic visit or by telephone. Carefully assess the need for the participant to come in for a clinic visit for taste/swallow tests and/or for adherence discussions.

If the participant comes into the CC for her routine clinic visit, collect her old CaD study pill bottles, assess adherence, and dispense new CaD study pills.

- If an estimated count was entered into WHILMA at the time she stopped taking her CaD study pills, replace it with the actual weight. Do not change the contact date when you enter the actual weight into WHILMA.

- If an estimated count was not done at the time she stopped taking her study pills, weigh the bottles and enter the weight into WHILMA. Use the date of the clinic visit as the contact date.

If switching formulations occurs at a non-routine clinic visit, collect her old CaD study pill bottles and assess adherence as you would for a routine clinic or contact and dispense new CaD study pills.

If the switch in formulations is made by telephone, ask the participant to stop taking her old study pills and to mail the old bottles back to the CC **as soon as she receives the new bottles**. CCs should provide participants with a self-addressed, stamped mailer. Mail the new study pill bottles to the participant immediately after the phone call. Ensure a CC staff person telephones the participants to confirm she received the new study pill bottle(s).

15.4.7 Selecting and Dispensing Study Pills for Remote Site Locations (Required)

A CC conducting follow-up visits at remote site locations must determine which procedures would best meet their specific needs. The options are to:

- Select the study pills in WHILMA in advance of a participant's scheduled clinic visit and dispense them to the participant at the clinic visit or

- Select the study pills in WHILMA after a participant's scheduled clinic visit and mail the study pills to the participant.

Either option will require the remote site to have the following supplies available: chewable tablets and swallowable pills for the CaD taste tests (to use before CaD randomization occurs), pill organizers, HRT Handbooks, consents for non-child resistant caps, non-child resistant caps, CaD consents, and the CaD Information Sheet.

15.4.7.1 Select the Study Pills before the Clinic Visit

Following are procedures that must be done at the main CC and the remote site:

Procedures at the Main CC:

- Use WHILMA to select the study pill bottle(s) for the participant's remote site clinic visit. To have the least effect on adherence, select the study pill bottle(s) either the evening before or the morning of the participant's scheduled clinic visit (at the remote site).

- Affix the participant's ID label to the study pill bottle(s), as usual.

- Carry the study pill bottle(s) to the remote site.

Procedures at the Remote Site:

- Store the study pill bottle(s) in a locked storage area at the remote site (i.e., do not store the study pill bottle(s) in the car).

- At the scheduled clinic visit, retrieve the previously dispensed study pill bottle(s) from the participant.

- Give the new study pill bottle(s) to the participant.

- Complete dispensation procedures in accordance with *Vol. 2, Section 15.4 - Study Pill Dispensing (Required)*.

- If the participant does not show for the scheduled clinic visit at the remote site, return the study pill bottle(s) to the main CC.

Procedures at the Main CC:

- Do an adherence collection for the participant's previously dispensed study pill bottle(s).
- If the participant did not show for her scheduled clinic visit, do an adherence collection for study pill bottle(s) not dispensed to the participant (indicating "0" adherence in WHILMA).
- If the participant did not show for her scheduled clinic visit and she is running out of study pills, from the main CC, select, label, and use overnight delivery service to mail the study pill bottle(s) to the participant.

15.4.7.2 Select the Study Pills after the Clinic Visit

Following are procedures that must be done at the remote site and main CC:

Procedures at the Remote Site:

- At the scheduled clinic visit, retrieve the previously dispensed study pill bottle(s) from the participant.
- Explain to the participant that her new study pill bottle(s) will be mailed (overnight delivery) from the main CC within 24 hours. Ask her to call the CC to report receipt of the study pill bottle(s).
- Complete dispensation procedures in accordance with *Vol. 2, Section 15.4 Study Pill Dispensing (Required).*

Procedures at the Main CC:

- Do an adherence collection for the participant's previously dispensed study pill bottle(s).
- Complete dispensation procedures in accordance with *Vol. 2, Section 15.4 – Study Pill Dispensing (Required).*
- Use overnight delivery service to mail the new study pill bottle(s) to the participant.

15.4.7.3 Strategies for Selecting and Dispensing Study Pills for Remote Site Locations

If the study pills are selected in WHILMA and labeled and the participant cancels the scheduled clinic visit, you must use your best judgment in this instance, depending on the situation (i.e., how soon can the participant reschedule the clinic visit). At the clinic's discretion:

- Mail the study pill bottle(s) to the participant or
- If the participant cannot reschedule within the week, do an adherence collection for the study pill bottles (indicating "0" adherence for the bottles). When the clinic visit is rescheduled, repeat the same procedures for dispensing at the remote site.

The decision to dispense open-label medications to a participant may be made during a scheduled remote site clinic visit or after an unscheduled remote site visit. Explain to the participant that the open-label medications will be mailed to her within the next 24 hours and she should begin taking them (as instructed) when she receives them. Select them in WHILMA and label the open-label medications at the main CC. Use overnight delivery service to mail them to the participant. If this is not the first time the participant is dispensed open-label medications, ask her to keep taking the open-label medications until empty and then start using the new open-label medications. Give her a postage-paid envelope to return the study pill bottle(s) to the main CC. Do an adherence collection for study pill bottle(s) not dispensed to a participant (indicating "0" adherence for the bottles).

If the participant wants to change CaD formulations, tell her that the changed formulation will be mailed from the main CC within 24 hours. Explain to the participant that she should begin taking them (as instructed) when she receives them. Select and label the new CaD formulation study bottle(s). Use overnight delivery service to mail them to the participant. Keep in mind that only a six month supply should be dispensed until the participant has been on the same formulation for one year. If the participant decides to change formulations, do an adherence collection for study pill bottles not dispensed to the participant (indicating "0" adherence for the bottles).

15.5 Selecting and Dispensing Problems (HRT/CaD) (Required)

A variety of situations or problems may arise when selecting and dispensing study tablet. With the exception of the HRT enrollment pill bottles, under no circumstances should you give a participant a bottle labeled with a bottle number other than the number assigned by WHILMA or the Clinical Coordinating Center (CCC). You are required to use the computer (WHILMA) to select study pills for *randomized* participants. If the computer is down, explain to the participant that you will mail her bottle to her when the computer is functioning again.

15.5.1 Abnormal Lab Results While On HRT Enrollment Pills

Participants may have abnormal or suspicious test results requiring follow-up while on the HRT enrollment pills. Abnormal tests results may include an abnormal pelvic exam, Pap smear, endometrial aspiration, transvaginal uterine ultrasound, clinical breast exam, or mammogram.

Follow the procedure below when you receive abnormal results:

- Ask the participant to stop taking her HRT enrollment pills until the abnormal results are resolved.
- Collect adherence information on the HRT enrollment bottle (or bottles) previously dispensed.
- Ask her to obtain appropriate follow-up evaluation and have results sent to the CC.
- Record the results of the follow-up evaluation on the appropriate form.
- If the participant is eligible to continue screening, start a second HRT enrollment period (see *Section 15.4.1.3 - Repeat HRT Enrollment Period*). Dispense a new bottle to the participant, indicating in WHILMA that the bottle is for a second enrollment period.

15.5.2 Bottle is Lost or Damaged Before You Dispense It (Required)

If the bottle selected for dispensing is lost or damaged and you cannot give it to the participant:

- Disable the bottle using the appropriate WHILMA option (see *Vol. 5, Section 7.3.3.1 - Managing Medication Inventory*).
- Re-run the selection function to select the next bottle.
- Dispense the selected bottle to the participant.
- Return the damaged HRT or CaD study pill bottle to McKesson, indicating when you found the damaged bottles. Returning the damaged bottle will help McKesson assess the type of damage problems you are finding and provide feedback to the drug manufacturer.

If you later find a bottle that you reported lost, do not dispense it to the participant. Return the bottle (which should already be disabled) to McKesson as described above.

15.5.3 Participant Has a Lost or Damaged Bottle (Required)

If a participant loses or damages a bottle you dispensed to her, conduct an adherence collection (estimated count or actual weight) for that bottle as a soon as she reports the loss or damage and dispense another bottle to her. Use the same procedure described under selecting and dispensing at the semi-annual or annual visits [see *Section 15.4.3 - Selecting and Dispensing HRT Study Pill Bottles at Semi-Annual and Annual visits (Required)* above] to select a new bottle number.

- Mail a new bottle in a padded envelope.
- If the previous bottle was damaged rather than lost, instruct the participant to return it immediately to the CC.

- Supply a self-addressed stamped mailer for mailing back the damaged bottle.
- Remind the participant that all bottles should be returned at the next visit.

If this occurs a second time for a participant, investigate the problem and take appropriate steps to resolve it.

15.5.4 Participant's Supply Runs Out (Required)

15.5.4.1 HRT Enrollment Pills

Run the *Enrollment Medication Reminder Phone Call Report (WHIP 0227)* in WHILMA to identify participants who will run out of enrollment pills during a specified time period. Select and dispense a second bottle as needed (see *Vol. 5 - Data System, Section 9 - Queries and Reports* for instructions on running reports). WHILMA calculates adherence from the weight of each bottle, the date of dispensation, and the date of adherence collection for that bottle.

15.5.4.2 Study Pills (HRT, CaD)

If a participant calls to ask for additional pills because her last bottle is empty:

1. Determine the date of the next regularly scheduled visit.
2. If the next visit is less than one week away, do not mail a new bottle.

   If the participant seems concerned, explain that by the time the bottle arrived, it would almost be time for the visit. Also, because of the cost and the potential for losing or being delayed in the mail, it is better to dispense the bottle in person.
3. If the next visit is more than a week away, determine why the participant has a study pill shortage. Possible explanations are:
   - lost or damaged bottle or pills
   - missing visit or visit done outside window
   - sharing of pills
   - improper dosings (over-medicating)
   - inadequate supply originally
4. If indicated, mail the appropriate bottle and have her return her old bottle(s) by return mail.

Do not allow participants to use the pill-mailing option as a means of avoiding a regular visit, unless absolutely necessary for retention (see *Section 16.4.1 - Strategies for Avoiding Missed Contacts*).

If the participant is over-medicating, it is important to know this and advise her against this. Inform your Clinic Practitioner (CP) and ask for further assistance in deciding whether to mail an additional bottle.

If the participant is sharing pills with someone else, it is unlikely that she will volunteer this information. If she does, strongly discourage any further sharing. Mail an additional bottle as described above after the participant has agreed not to share.

15.5.5 No Bottles Available (Required)

If all of the bottles identified by WHILMA for dispensing to a participant are missing, contact the CCC Data Coordinator immediately. If WHILMA displays an "insufficient inventory" message when you attempt to select a study pill bottle, notify McKesson immediately by phone, eMAIL, or fax to order additional study pill supplies. Tell the participant that you will be mailing the bottle to her. Also review your ordering procedures with McKesson to determine why you did not have an adequate supply of bottles in stock. Review the *Drug Inventory* report (*WHIP 0032*) from WHILMA at least quarterly and use it to monitor your study pill supply.

15.5.6 Participant Drops Out (Required)

When a participant is told or asks to discontinue study pills (or informs the CC that she is dropping out), collect her study pill bottle(s) and adherence data immediately and complete the appropriate WHI forms (which may include *Form 54 - Change of Medications* and/or *Form 7 - Participant Status*). Refer to *Section 17 - Retention* for additional information on participant status.

15.5.7 Transferred Participants (Required)

During the course of the study, participants randomized at one CC may transfer to another CC. Select and dispense study pill bottles to participants transferred to your clinic as you do for routine participants. See *Section 17.5 - Transfer of Participants Between Clinical Centers* for procedures on transferring and receiving participants.

15.5.8 Reactivated Participants (Required)

Select and dispense study pills to reactivated participants as you do to active participants. When you schedule a reactivation visit for a participant, check the participant file to be sure there is a label for the bottle. See *Section 17.4.5 - Reactivation of Participants with Changes in Participation Status*.

15.6 Study Pill Adherence Monitoring (Required)

The CC must accurately monitor the participant's adherence to the HRT and/or CaD interventions. Non-adherence to the daily pill regimen may dilute any true difference between the intervention arms.

The CC assesses the participant's adherence to taking study pills by weighing returned study pills (HRT) or study pill bottles (CaD) or by self-report of the number of estimated pills remaining in the bottle if bottles are not returned. However, CCs should encourage the participant to return the old bottle(s) by mail using a prepaid mailer supplied by the CC. Actual weight is preferred over estimates.

If study pills are dispensed to a participant on a semi-annual basis (every 6 months), adherence data should be entered in WHILMA for that participant every 6 months. If study pills are dispensed to a participant on an annual basis (every 12 months), adherence data should be entered in WHILMA for that participant every 12 months.

Clinical Centers that dispense an annual supply at annual visits will still be expected to assess adherence at semi-annual contacts. Do not enter this estimate into WHILMA. Request all bottles at the next annual visit.

From the adherence data, the CCC will calculate pill consumption rates over time for each participant. Mean study pill consumption rates are reviewed semi-annually by the WHI Council, Data and Safety Monitoring Board, and NIH.

15.6.1 Purpose

The purpose of monitoring study pill adherence is to:

- establish eligibility at SV3 (for HRT participants)
- determine participant's actual pill consumption rate
- distinguish participants with good adherence from participants with poor adherence when implementing focused programs to boost adherence
- determine reasons why participants don't take their study pills
- determine how participants make up for missed pills (if at all)

15.6.2 Adherence Assessment

Adherence is determined by weighing the returned study pills (HRT) or study pill bottle (CaD). The procedure is similar for all types of clinic contacts. *Figure 15.5 - Study Pill Adherence Assessment For Follow-Up Procedures* provides a flow chart for making decisions about appropriate adherence assessment procedures.

15.6.2.1 Approach to Participant (Required)

Use the following procedures in assessing the participant's study pill adherence. If participants ask why they must return unused pills and empty bottles, you may tell them:

- to perform quality assurance checks
- to check for deterioration of the unused pills
- to comply with FDA requirements for returning investigational drugs to the study center

To ensure useful adherence information is obtained:

- do not tell participants that you measure pill adherence by weighing returned study pills or study pill bottles
- do not weigh the study pills or study pill bottles in front of the participant
- do not confront participants with pill weight or count information as the basis for admonishing or encouraging them towards better adherence
- assume that the participants take the pills as prescribed unless they volunteer or acknowledge on self-report that they are not taking them

If a participant asks if you are weighing or counting the pills, do not deny it. You might simply say "I have noticed that there seem to be more pills left in the bottle than I expected," and then proceed to explore the reasons for non-adherence. If appropriate, you might say, "It appears that you are taking most of your pills as you should."

When dispensing study pill bottles, explain to the participant that you want her to bring in any unused pills in the original bottle, pill organizers containing pills, and any empty study pill bottles at the next visit. You may affix a sticker to the bottle as a reminder for the participant to return her study pill bottle at each clinic visit. A reminder postcard will also help the participant remember to bring in all study pill bottles she has.

15.6.2.2 Weighing Procedures (Required)

The weight of the returned HRT or open label study pills, and CaD study pills and bottles, rather than pill count, will be used to calculate adherence. (Study pill bottles are not weighed before they are dispensed). If the bottles are not returned, estimated pill counts are used to calculate adherence. Do not be concerned about weight differences between study pill bottles. WHILMA will calculate adherence appropriately. Any perceived differences between the weights of the study pill bottles should not be discussed with participants.

1. Equipment/Supplies

- OHAUS Portable Advanced Electronic Balance (Model CT1200)
- Two calibration masses: 1000 g weight and 500 g weight
- OHAUS Instruction Manual: Read the accompanying manual before you use the scale
- Pill scoop

Service Information:

If the Troubleshooting section does not resolve or describe your problem, contact an authorized OHAUS Service Agent (1-800-526-0659). In New Jersey, call (201) 377-9000. Contact the CCC to request a loaner.

a. Initial Scale Set-Up

Selection of Unit Weight (refer to pages 21 and 22 of the OHAUS Instruction Manual): the scales are set up at the factory to read in "gram" units. **Do not change this setting**.

Selection of Platform: remove the cup weighing container from the scale and use the accompanying platform attachment instead.

b. Daily Set-Up

Scale Set-Up: with nothing on the platform, press the "On Tare" button. Allow at least 5 minutes for the balance to temperature stabilize before using.

Calibration: the OHAUS balance is calibrated in two ways before shipment: for Span and Linearity. Span calibration resets the balance weighing range using two weight values: zero, and a weight value at or near the balance's capacity. Linearity calibration is performed before shipment and should not need to be repeated. If determined that linearity calibration is needed, follow the procedures given in the OHAUS Instruction Manual (page 18).

Calibrate the scale each day before it is used following the procedure below. Span calibration should also be done each time you move the scale and after rough handling.

Span Calibration: (refer to page 17 of the OHAUS Instruction Manual):

- Remove all weight from the platform. Have the 1000 g weight available.
- Press and hold "On Tare button" until CAL is displayed, then release it. The balance will display SPAN.
- Press The "On Tare" button again. When released, "C 0 g" will be displayed. This indicated that no weight should be on the platform.
- Press "On Tare" for the third time.
- When it is released, the display window will show "-C-" briefly, then "C" followed by the value of the calibration mass (1000 g) to put on the platform. DO NOT disturb the balance or place anything on the platform when "-C-" is displayed. The balance is waiting for a stable weight reading and disturbances will result in improper calibration.
- Place the 1000 g weight on the platform, then press the "On-Tare" button.
- The display window will show "-C-" while the balance re-calibrates itself. DO NOT REMOVE the 1000 g weight at this point. When the balance returns to the normal weighing mode (the Unit Indicator will appear in the display window), span calibration is completed. Remove the 1000 g mass from the platform and store.
- To exit the calibration mode, press "Off mode" until END is displayed. Press "On Tare" to return the balance to normal weighting operations.
- Note: the scale is extremely sensitive and will drift with any additional motion in the area. Take the reading as soon as the value seems to have stabilized. Drift will also occur if the mass is left on the platform for a longer period of time.

2. Weighing Study Pills

The procedures for weighing returned HRT and CaD study pills are different in one way, in that you

- weigh HRT pills **without** the bottle and
- weigh CaD pills **with** the bottle and cap.

The actual weighing procedures cannot be monitored by WHILMA, therefore WHILMA will not notify you if you use incorrect weighing procedures. HRT adherence assessed on weights that include the HRT bottle will be inappropriately low. To remind staff of the weighing procedures, post the Study Pill Weighing Procedures (see *Figure 15.4*) near the scale.

a. Weighing HRT Study Pills

Weigh all returned **HRT or open label study pills (without the bottles)**, including HRT study pills from unopened bottles, and from pill organizers.

- With an empty scale platform, press "On Tare".
- Place the empty pill scoop on the platform. Its weight will be displayed.
- Press "On Tare" again. A zero will be displayed.
- Pour the study pills into the scoop and read the weight. The weight displayed will be that of the study pills alone.
- Key-enter the weight of the pills into WHILMA and record the adherence rate the appropriate line of question 5, *Form 10 - HRT Management and Safety Interview*.
- If you have multiple HRT pill weights to assess, empty the scoop, add the next study pills, and repeat step #5. (The tared weight will remain in memory until "On Tare" is pressed again.)
- To change to weighing CaD bottles, first clear the memory by pushing "On Tare" or turn the scale off. Then follow the procedures for weighing CaD bottles below.

Reference: OHAUS Scale Instruction Manual, page 12.

a. Weighing CaD Bottles

- Weigh the swallowable CaD pill **bottles** (leaving the pills in the bottle) and the chewable CaD tablet **bottles** using the same procedure. WHILMA knows which formulation is being collected by the bottle ID.
- Weigh all returned CaD study pill **bottles** returned by the participant, including CaD study pills from unopened bottles, and from pill organizers. **Weigh CaD bottles** WITH the original child-resistant caps. Keep an extra CaD child-resistant <u>outer</u> shell cap near the scale in case the original outer cap has been removed. If the child-resistant cap was <u>replaced</u> with a non-child resistant cap or the outer shell cap was removed, place the outer shell cap on the scale when the bottle is weighed. (You don't need to attach the shell to the bottle cap; instead lay the shell on the scale platform.)
- Wait until the scale indicator appears before reading the displayed weight. (This should take no more than 5 seconds.) When the indicator appears, the reading is stable. Note: The scale is extremely sensitive and will drift with any additional motion in the area. Take the reading as soon as the value seems to have stabilized. Drift will also occur if the mass is left on the platform for a longer period of time.
- If weighing multiple bottles, wait for the scale to read "0 g" before putting another bottle on the scale.

3. Enter Adherence Data (HRT/CaD)

Enter the adherence information into WHILMA as described in *Vol. 5, Section 7.3.3.5 - Medication Adherence.* If you are not able to enter the weight directly, write the date and the weight directly on the bottle for future reference.

4. Estimated Pill Count When Bottle is Not Available (HRT/CaD)

CCs need to make every effort to obtain bottles from participants. When this is not possible an estimated count is an acceptable alternative. Obtain the adherence data for each bottle not returned by asking the participant how many pills remain in each unreturned bottle. If the participant does not know the number remaining, ask her to estimate the number remaining (e.g., is the bottle 3/4, 1/2, or 1/4 full). (See *Section 15.6.2.6 - Bottles Not Returned (Required)* for more details.)

Enter the estimated count into WHILMA as described in *Vol. 5 - Data System, Section 7.3.3.5 - Medication Adherence Collection* and in the addendum to the v.35 upgrade notes. If you later receive the bottle on which you estimated the count, weigh the bottle or pills, delete the estimated count, and enter the weight into WHILMA.

Figure 0.4

STUDY PILL WEIGHING PROCEDURE

HRT - Weigh pills **without** the bottle

1. With an empty scale platform, press "On Tare".
2. Place the empty pill scoop on the platform. Its weight will be displayed.
3. Press "On Tare" again. A zero will be displayed.
4. Pour the study pills out of the bottle into the scoop and read the weight. The weight displayed will be that of the study pills alone.
5. Key-enter the weight of the pills into WHILMA and record the adherence rate *Form 10 -HRT Management and Safety Interview*.
6. If you have multiple HRT pill weights to assess, empty the scoop, add the next study pills, and repeat step #5. (The tared weight will remain in memory until "On Tare" is pressed again.)

CaD - Weigh pills **with** bottle and cap.

1. Clear the memory by pushing "On Tare" or turn the scale off then on again. A zero will be displayed.
2. Place the bottle with the cap on the scale. If the cap is a non-child resistant cap, see procedures in *Vol. 2, Section 15.6.2.2 - b) Weighing CaD Bottles.*
3. Key-enter the weight into WHILMA and record the adherence rate on *Form 17 - CaD Management and Safety.*
4. If you have multiple CaD bottle weights to assess, repeat step 2.

Reference: *OHAUS Scale Instruction Manual*, page 12.

15.6.2.3 HRT Enrollment Adherence (Required)

When assessing HRT enrollment adherence, use one of the following dates as the encounter date in WHILMA:

- If the participant brings the bottle to the visit, use the date the CC collects the HRT enrollment bottle from the participant.
- If the participant loses the bottle and/or pills, use the date the participant contacts the CC to report that she has lost the HRT enrollment bottle and/or pills in the bottle.
- If the participant runs out of pills, use the date the participant contacts the CC to report that she ran out of HRT enrollment pills.

Do not use the date the participant says she lost the bottle or ran out of pills. Use the date she contacts the CC.

If a participant is ineligible due to the HRT enrollment adherence criterion, you can repeat the enrollment one time only. See *Section 15.4.3 - Repeat HRT Enrollment Period*.

To assess and document enrollment adherence:

- Determine adherence by weighing the enrollment bottle (refer to weighing procedure above).
- Enter the bottle weight into WHILMA as described in *Vol. 5 - Data System, Section 7.3.3.5 - Medication Adherence Collection* (released initially in the addendum to the WHILMA v.35 upgrade notes).
- The database will determine the participant's adherence eligibility based on the number of days between dispensing and adherence collection, and the number of pills returned as calculated from the bottle weight.
- Empty the weighed pills into the HRT discard container. See *Section 15.3.4 - Returning Study Pills to Mckesson (Required).*

15.6.2.4 HRT and CaD Semi-Annual and Annual Follow-Up Contacts (Required)

In general, the sooner the study pill bottles are collected from the participants, the more likely the data will be accurate.

1. When the participant returns used bottles at a CC visit, do the following:

    - Take the returned bottles and the participant's file with you when you leave to get the new bottles of study pills for the participant. If the participant asks you why you are taking the bottles with you, tell her that it is to cross-check the bottle ID and name on the old and new bottles. See also *Section 15.6.2.1 - Approach to the Participant*.
    - Verify that the bottle ID number on the returned bottles matches the bottle ID number from the file.
    - Follow the procedures described in *Section 15.6.2.2 - Bottle Weighing Procedure To Weigh Pills and/or Bottles.*
    - Enter the weight into WHILMA as described in *Vol. 5, Section 7.3.3.5 - Medication Adherence Collection.*
    - Empty the weighed pills into the HRT and/or CaD discard container. See *Section 15.3.4 - Returning Study Pills to McKesson*.
    - When assessing multiple bottles the participant returned at the same time, be careful to record the correct weight for the corresponding bottle number.

2. When the participant is dispensed a 6-month supply at her AV1 and her next contact (SA2) is conducted by phone, do the following:

   - During the phone contact, ask the participant to estimate the number of study pills remaining in her study pill bottle(s) and record her estimate on *Form 10 - HRT Management and Safety Interview* or *Form 17 CaD Management and Safety Interview*.

   - Create an adherence collection encounter (*Task 951* in WHILMA). The contact date of *Task 951* should be the date of the phone contact where the estimate was obtained from the participant. Enter the estimated count from *Form 10 - HRT Management and Safety Interview* or *Form 17 - CaD Management and Safety Interview*.

   - Tell the participant you will mail her next supply of study pills along with a pre-paid mailer to return the study pill bottles she currently has. Ask her to continue to take study pills out of the current study pill bottle until she receives the new supply. Tell her to stop taking study pills out of the old study pill bottle and start taking study pills out of the new study pill bottle when she receives the new supply. (Note: Use of prepaid mailers is strongly recommended, but not required.)

   - Ask her to mail the old study pill bottles back to the CC at her earliest convenience. Suggest she mark an "X" through the label of the old study pill bottle.

   - When you receive the old study pill bottles at the CC, weigh them following the appropriate procedures for CaD and HRT.

   - Go into the *Task 951* created for the corresponding bottle(s) on the date of the phone contact and delete the estimated count. Enter the actual weight of the pills (HRT) or bottles (CaD). Do not change the contact date when you enter the actual weight into WHILMA.

   If the participant keeps the bottles until her next clinic visit, ask the participant to put an "X" through the label of the old study pill bottle(s) to ensure she does not get the old and new study pill bottle(s) mixed up.

   If the study pill bottles are not collected, obtain an estimated count to enter into WHILMA. Take any appropriate steps to collect the study pill bottle(s) from the participant (e.g., give) her a pre-paid mailer to mail the study pill bottle(s) back to the CC. If this is not feasible, ask her to return the study pill bottles at the next contact.

15.6.2.5 HRT and CaD Bottles Returned by Mail (Required)

When assessing adherence on bottles returned by mail, use the following procedures (see *Figure 15.5 - Study Pill Adherence Assessment (For Follow-Up Contact)*):

- If the participant returns used bottles by mail, follow the steps for bottles returned at visits to weigh the study pills and/or bottle.
- If the participant reports to the CC by phone before mailing the bottle, use the date of the phone call as the adherence date.
- If she mails the bottle without having called, use the date the bottle is received by the CC.
- If a pill estimate was previously done on the returned bottle, delete the previously entered estimated count from the database and key-enter the weight.

15.6.2.6 HRT and CaD Bottles Not Returned (Required)

If a participant does not bring the used study bottle to SV3 or the routine follow-up visits (see *Figure 15.5 - Study Pill Adherence Assessment (For Follow-up Contact)*, encourage her to mail the bottles and remaining pills back to the CC and send her a prepaid mailer. At the contact, use the following procedures:

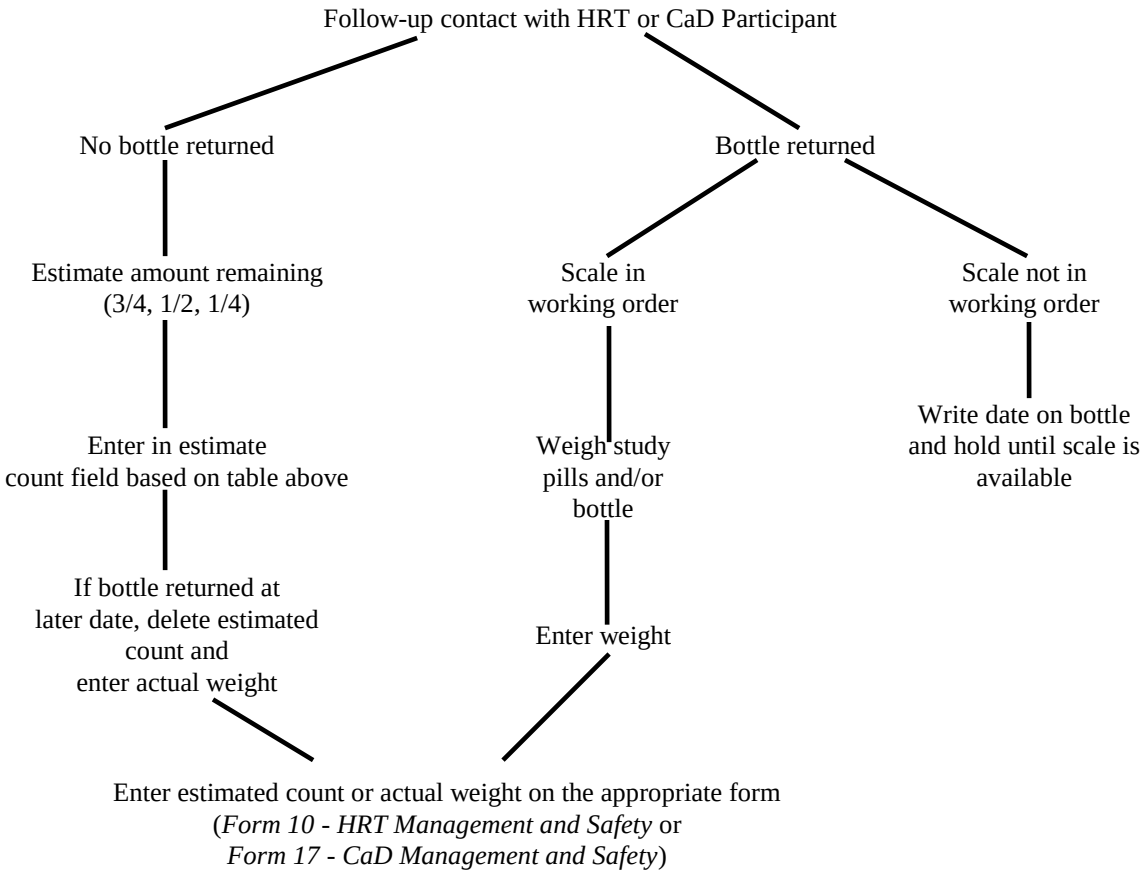
- Determine the last bottle number dispensed to the participant by reviewing the *Dispensations Report (WHIP 0232)*.

  Obtain the adherence data for each unreturned bottle by asking the participant how many pills remained in each unreturned bottle. If the participant does not know the number of pills remaining, ask the participant to estimate the number remaining (e.g., is the bottle 3/4, 1/2, or 1/4 full). Use interviewing techniques (see *Section 2 - Clinical Center Guidelines*) to get the participant to give you an estimate. Note that a bottle with the full complement of study pills may not be filled to the top with pills. Ideally, pill estimates should account for this fact. Use the following table as a guideline for converting their responses:

Response	# of HRT Pills Remaining	# of HRT Open Label Pills Remaining	# of HRT Enrollment Pills Remaining	# of CaD Chewable Tablets Remaining	# CaD Swallowable Pills Remaining
"Full" bottles	215	100	50	215	430
"Half full"	110	50	25	110	215
"Almost empty"	25	10	5	25	25

- Enter the estimated count into WHILMA described in *Vol. 5, Section 7.3.3.5 - Medication Adherence Collection*.
- Tell the participant not to take any more study pills from the used bottles.
- Provide the participant with a self-addressed stamped mailer and ask her to mail the used bottles to the CC, or ask the participant to return the bottles at the next visit. Collect actual adherence information when these bottles are received.
- If a participant reports losing a bottle, conduct an adherence collection immediately. Have her estimate the number of pills left in the bottle when she lost it.

Figure 0.5
Study Pill Adherence Assessment (For Follow-Up Contact)



15.7 Study Pill Problems

15.7.1 Overdose

The CCC provides each CC and the nation-wide Poisindex with a study-wide statement regarding study pills used in the HRT and CaD trials. The statement includes the chemical names and dosages of all study pills used along with the possible number dispensed. Attached to the statements are the Poisindex listing for estrogens and progestins or calcium and vitamin D, as well as a list of the CCs, their phone numbers, addresses and Principal Investigators (PI). Clinical Centers may copy and distribute this to their local poison control, emergency rooms in the area, and any other agency that may be involved in an overdose situation.

In general, overdose of hormones has not been found to result in life-threatening situations and conservative treatment has been sufficient. Symptoms usually consist of nausea and/or vomiting.

Overdose of calcium and vitamin D supplements may rarely result in a condition known as hypercalcemia. Participants may describe deep bone or flank pain, loss of appetite, nausea, vomiting, thirst, constipation, a tendency to trip or to drop things, changes in heart rhythm or lethargy. Psychosis is also a manifestation of hypercalcemia. Vitamin D overdose symptoms are identical to those of calcium overdose.

Use the guidelines below to manage all calls related to study pill overdose.

15.7.1.1 Treatment

Women's Health Initiative CC staff should not provide or recommend treatment for WHI study pill overdose. Treatment of an actual or suspected overdose should be provided by one of the following resources: a local Poison Control Center, a local **emergency** center, or the participant's primary physician. Each CC should decide to which resource these calls will be referred and then create an internal procedure for such referral. Treatment guidelines should be available in your CC's Internal Manual for reference by staff or these community resources.

15.7.1.2 Unblinding

Standard treatment for overdose of HRT or CaD study pills may be initiated per the Poisindex recommendations with out unblinding the participant's study arm. There may be extreme circumstances, however, where unblinding is deemed necessary. In these cases, the CC consulting gynecologist CC medical director, or PI should be notified and the unblinding procedure initiated (see *Section 5.6 - Unblinding* for HRT and *Section 7.3.4 - Unblinding* for CaD).

15.7.1.3 Managing Overdose Calls

Use the following procedures to manage a call to the CC regarding study pill overdose:

1. Inform the caller that you need some information and that you will refer the call to the local Poison Control Center, the local emergency center, or the participant's primary physician (depending on your CC's policy).
2. Document the following information:
    - name and telephone number of caller
    - name of WHI participant
    - name and age of person (if not the participant) who consumed the study medication pills
    - approximate number of pills consumed
    - WHI bottle number

1. Refer the call to the local Poison Control Center, local emergency center, or the participant's primary physician (depending on your CC's policy).
2. If study pill unblinding is deemed necessary, ask the local Poison Control Center, the local emergency center, or the participant's primary physician to call the CC consulting gynecologist, medical director, or PI.
3. Document the incident in the participant's file.
4. Present the overdose case at the next CC staff meeting. This will be useful in reviewing and revising appropriate CC policies.

Note: If you refer overdose calls to the participant's primary physician, you may need to provide WHI treatment protocol guidelines to the primary physician.

15.7.2 Serious Adverse Experiences (SAEs)

Serious Adverse Experiences (SAEs) are reported and monitored through WHI outcomes processing and analysis. The Food and Drug Administration (FDA) has approved this strategy for the WHI HRT and CaD trials. Clinical Centers should consult with their local IRBs to determine if additional reporting and monitoring is required locally.

15.8 Managing Adherence

Adherence to study pills is an important part of the WHI study design and critical for testing the study hypothesis. Assess for and act on adherence problems at all participant contacts. See *Section 17.2 - CC Activities for Retention Challenges* for retention activities related to adherence, reasons for poor adherence, and activities to ensure full adherence.

15.8.1 Intensive Adherence Program (Required)

The Intensive Adherence Program is a required series of special participant contacts without data collection, aimed at improving poor adherence and dealing with pill adherence problems. Intensive Adherence Program contacts are made with participants who report low adherence levels or because of CC staff referral for adherence problems. The number, frequency, and content of the contacts vary according to participant need and CC staff discretion. Refer to *Section 17.2.5. - Intensive Adherence Program* for more detail on this important adherence management strategy.

Table 0.2
WHI Placebo Ingredients (PERT Placebo)

Core Ingredients:	Input/Tablet	Representative Batch Formula 100,000 Tablets
Polyethylene Glycol, 8,000, NF	28.8 mg	2.88 kg
Lactose, NF	86.4 mg	8.64 kg
Magnesium Stearate, NF	0.60 mg	0.06 kg
Talc, USP	4.20 mg	0.42 kg
Theoretical Core Weight - 120 mg		
Coating Ingredients:[A]		
Seal Coat		
Polyethylene Glycol Type 20,000	0.30 mg	0.03 kg
Alcohol, Denatured, 23A[B]	—	0.024 kg
Glyceryl Monooleate	0.150 mg	0.015 kg
Shellac Solution, White, 4# Cut[C]	5.62 mg	0.56 kg
Calcium Sulfate, NF Anhydrous	10.7 mg	1.07 kg
Inert Filler Coat		
Microcrystalline Cellulose, NF	7.32 mg	0.73 kg
Sucrose, NF	97.6 mg	9.76 kg
Titanium Dioxide, USP	0.10 mg	0.01 kg
Purified Water, USP[B]	—	3.80 kg
Placebo Filler Coat		
Povidone, USP	1.56 mg	0.16 kg
Purified Water, USP[B]	—	5.61 kg
Sucrose, NF	102 mg	10.2 kg
Color		
Purified Water, USP[B]	—	0.94 kg
Sucrose, NF	18.9 mg	1.89 kg
Titanium Dioxide, USP	0.45 mg	0.045 kg
Polish		
Carnauba Wax, NF	0.16 mg	0.016 kg
Mineral Spirits, Odorless[B]	—	0.033 kg

[A] These quantities per tablet represent theoretical amounts of coating materials applied. The actual amounts may vary depending on coating efficiency, tablet characteristics and processing conditions.

[B] Removed during processing.

[C] This represents the amount of solution at a theoretical solids content of 34.8% w/w.

Table 0.3
WHI Placebo Ingredients (ERT Placebo)

Core Ingredients:	Input/Tablet	Representative Batch Formula 100,000 Tablets
Color		
Purified Water, USP[A]	—	0.97 kg
Sucrose, NF	24.7 mg	2.47 kg
Titanium Dioxide, USP	1.72 mg	0.17 kg
Polish		
Carnauba Wax, NF	0.12 mg	0.012 kg
Mineral Spirits, Odorless[A]	—	0.025 kg

Table 0.4
WHI Chewable CaD Ingredients

Chewable Active	Chewable Placebo
Calcium Carbonate, USP	Sugar, Compressible, NF
Starch, Modified Corn, NF	Starch, Modified Corn, NF
Confectioners Sugar, NF	
Talc, USP	Contrasweet Powder (MM32)
Light Mineral Oil, NF	Peppermint Powder, 20% Spray Dried
Sodium Hexametaphosphate, FCC	Magnesium Stearate, NF
Peppermint Powder, 20% Spray Dried	
Vitamin D3, Dry Type, 100 CWS	

[A] Removed during processing.

Table 0.5
WHI Swallowable CaD Ingredients

Swallowable CaD Active	Swallowable CaD Placebo
Oyster Shell Granulation	Lactose Anydrous NF
Corn Starch NF	Microcrystalline Cellulose NF
Calcium Stearate NF	Magnesium Stearate NF
Talc USP	FD&C Blue #1 Aluminum Lake
Sodium Starch Glycolate NF	D&C Red #30 Talc Lake
Vitamin D3	FD&C Yellow #6 Aluminum Lake
Coating Solution Solids	Coating Solution Solids
Carnauba Wax NF	Carnauba Wax NF

Section 15
Medications (Study Pills)

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SECTION 16

FOLLOW-UP CONTACTS

INTRODUCTION

Follow-up contacts with Women's Health Initiative (WHI) participants occur to address safety issues (Clinical Trial [CT] participants only), collect follow-up data, follow participants for study outcomes, and promote retention. These contacts provide an opportunity for Clinical Centers (CCs) to continue a professional, caring relationship with the participant throughout the duration of the study. The frequency and type of follow-up contacts depend on the study component and include the following:

- Early Adherence and Safety contact (Hormone Replacement Therapy [HRT] and Calcium and Vitamin [CaD]).
- Semi-annual contacts (CT).
- Annual visits (CT) and third-year visit (Observational Study [OS]).
- Annual mail contacts (OS).
- Annual newsletters at six months after anniversary of enrollment (OS).
- Semi-annual newsletters at approximately five and ten months after the anniversary of randomization (CT).
- Non-routine contacts (CT and OS).

Required follow-up tasks for each study component are identified in *Vol. 1 - Study Protocol and Policies, Table 1-A1.2 - Frequency of Collection*. The target dates for the routine follow-up contacts (visits, phone calls, mailings) and newsletter mailings are based on the randomization date to HRT or Dietary Modification (DM) or enrollment date for OS. Changes in participant involvement due to symptoms or other factors do not alter these target dates. When a participant discontinues any of the interventions, follow-up continues on a semi-annual or annual basis, as appropriate.

This section describes the required and recommended procedures for carrying out routine and non-routine follow-up contacts in all components of WHI.

16.1 Early Adherence and Safety Telephone Contact (HRT and CaD) (Required)

Clinical Center staff make an early phone call to each woman after randomization to HRT or CaD:

- HRT: The call should be made **six** weeks after randomization with a target window of two weeks (± 14 days) on either side of the target date.
- CaD: The call should be made **four** weeks after randomization with a target window of two weeks (± 14 days) on either side of the target date.

The purpose of this contact is to address early adherence and safety concerns. *Form 10 - HRT Management and Safety Interview* or *Form 17 - CaD Management and Safety Interview*, as appropriate, is administered as a phone interview. The purpose of the interview is to check that women in the HRT or CaD are continuing and tolerating the study pills, and that they are having no serious symptoms. The participant's adherence to the pill-taking schedule, by participant estimate, and her willingness to stay on schedule are also assessed. She is supported in her efforts to date, and appropriate referrals are made. This early encouragement has been shown to markedly enhance adherence.

Each CC can decide on the appropriate staff to conduct this phone contact, but the staff must be appropriately trained and certified. Interviewers will refer decisions about possible serious concerns to an appropriate retention specialist as soon as possible. Medical issues should be referred to a Clinic Practitioner (CP).

16.1.1 Preparation for the Telephone Contact

Each week, print the following two reports to identify HRT and CaD participants who need a phone contact:

- *WHIP 0781 - Participants Due for 6-Week Phone Call (HRT).*
- *WHIP 1320 - CaD Participants Due For a 4-Week Phone Call.*

For each participant to be contacted, print *WHIP 0441 - Personal Information Update* and prepare a *Form 10 - HRT Management and Safety Interview* or *Form 17 - CaD Management and Safety Interview*, as appropriate. Prepare to do several phone calls in any one phone session to streamline this activity. It may also be helpful to have participants' files and contact notes available while conducting the calls.

16.1.2 Conducting the Telephone Contact

Start the call attempts near the beginning of the target window to assure that you will be able to contact the participant within the target window (2 weeks on either side of the target six-week date for HRT or the target four-week date for CaD). Frequently, you will not be able to complete all the contacts you set out to do in one sitting. If you are unable to complete a phone call at a particular time and day, try calling at other times and days. A grid for recording the date and time of all phone call attempts is recommended to track this information. (See *Figure 17.1 - Sample Form to Track Contact Attempts*.) Conduct the phone call even if the date is beyond the target window. However, if the date falls within the target window for the first semi-annual contact, conduct the semi-annual contact instead and mark the visit type as semi-annual number one (see *Section 16.4.1 - Missed Contacts*).

16.1.2.1 Introduction and Personal Information Update (Required)

Begin the phone call by introducing yourself and the purpose for the call. The following is an example of what you might say:

"Hello, Mrs./Miss/Ms. (participant's last name). This is (your name) from the Women's Health Initiative at (your CC name). I am calling to find out how you are doing with your study pills and to answer any questions you may have. This will only take about 5-10 minutes. Is this a good time for you to talk?"

If the participant is willing to continue the interview, update and/or confirm her address, telephone number, and other contact information on *WHIP 0441 - Personal Information Update*. If the "father's last name" item is blank on *WHIP 0441*, ask the participant for her father's last name and record it in the space provided. You can inform the participant that this information will be kept confidential and helps the WHI staff to stay in contact with her. (See *Section 16.3.3.6 - Personal Information Update*.)

If the participant says this is not a good time to talk, schedule the telephone contact at a mutually convenient time, ideally, within the target window.

16.1.2.2 Safety Interview (Required)

Complete *Form 10 - HRT Management and Safety Interview* or *Form 17 - CaD Management and Safety Interview*, as appropriate, using the script on the form. Document the participant's responses to the appropriate safety items (e.g., hysterectomy status, specific symptoms, new medical conditions or medications), other concerns, and pill-taking routines. Refer to the interviewing guidelines in *Section 2.11 - Interviewer Procedures* as needed.

Review the participant's responses to the safety and adherence questions. Respond to participant questions and make recommendations based on the following informational resources:

- **HRT**: *Section 5 - HRT, Form 10* form instructions, *HRT Handbook* and the *HRT Question and Answers for CC Staff* in *Appendix G.1.2 - HRT*. If the HRT participant reports any of the conditions, symptoms, or medications listed below, refer her to the CP as soon as possible:
  - Hysterectomy, endometrial hyperplasia, high triglycerides, blood clot to leg or lung, melanoma, heart attack, stroke, or meningioma.
  - Vaginal bleeding or breast changes.
  - Use of anticoagulants or hormones (estrogen, progesterone, testosterone, tamoxifen).
  - Any other serious health questions or symptoms.
- **CaD**: *Section 7 - CaD, Form 17* form instructions, *CaD Handbook*, and *CaD Questions and Answers for CC Staff* in *Appendix G.1.1 - CaD*. If the CaD participant reports any of the conditions, symptoms, or medications listed below, refer her to the CP as soon as possible:
  - Hypercalcemia
  - Kidney problems (such as kidney or bladder stones)
  - Use of > 1,000 IU vitamin D daily
  - Use of calcitriol
  - Any other serious health question or symptoms

Discuss strategies for improving adherence and/or make appropriate referrals to CC staff specializing in adherence and retention issues (e.g., to Intensive Adherence Program). Refer to *Section 17 - Retention* and *Section 17.2.5 - Intensive Adherence Program*.

If the CaD participant indicates problems with tolerating the CaD study pills (e.g., because of its taste, size, or other characteristics) reassure her that she can switch to the other form at her next routine contact. If the participant indicates she is unwilling to wait that long, or has already stopped taking the study pills, explore with her the possibility of switching to the other form immediately. If she is willing to switch, follow procedures outlined in *Section 15.4.5 - Selecting and Dispensing CaD Study Pills*.

16.1.2.3 Concluding the Phone Call

At the end of the call, remind the participant to:

- Continue recording in *Form 53 - HRT Calendar* (if she has a uterus) and to bring the completed form to her next appointment (HRT only).
- Continue taking her study pills every day.
- Bring her study pill bottles (empty or not) and pill organizer with remaining study pills to her next appointment.

Thank the participant for her time *("You are helping us to get the answers to some very important women's health questions"*) and remind her of her next clinic visit or semi-annual contact.

Finally, forward the participant's forms to data entry.

16.2 Semi-Annual Contact (CT only) (Required)

Semi-annual contacts are conducted for all CT participants. The target date for semi-annual contacts is six months after randomization and six months after each randomization anniversary. The target window is ± 2 weeks (± 14 days) on either side of the target date.

The purpose of the semi-annual contact is to:

- Promote rapport with the participant and foster her continued interest in the study.
- Collect updated contact and medical information, including information on potential outcomes.
- Obtain current signatures on release of medical records forms.
- Collect information on safety concerns and symptoms (HRT, CaD).
- Assess and promote medication adherence and dispense a new supply of study pills (HRT, CaD).
- Schedule the next routine visit.

For HRT participants only, an in-person visit is required for the first semi-annual contact (SAV1). For HRT and CaD participants, all subsequent semi-annual contacts may be either an in-person visit, or a telephone call together with mailed forms and study pills as needed. For DM only participants, the SAV1 and all subsequent semi-annual contacts may be a visit, a phone call, or a mail contact. Each CC must decide what method of contact it will use for ongoing CT semi-annual contacts and develop procedures to coordinate and track participants appropriately. Consider when a participant would benefit from a visit rather than a contact so that issues of adherence, retention, and safety can be more directly addressed. Regardless of the method of contact chosen, all required activities must be completed. The "visit" method of contact is outlined below as an example.

16.2.1 Preparation for a Semi-Annual Visit

Print out a semi-annual visit plan *WHIP 0144 - Tasks Required at Visit* for the participant. This will list all the required WHI activities for that contact. Use of a semi-annual contact checklist that lists all WHI-required and CC-specific semi-annual contact activities is recommended (see model in *Vol. 2, Appendix E.4.6 - Model Semi-Annual Contact Checklist*). Each CC can design a checklist to best fit its own operations. Designate one person to review the checklist before the participant leaves the CC to be sure you have completed all the activities.

16.2.1.1 Two Weeks Before a Semi-Annual Visit

Two weeks before the semi-annual visit, mail the participant a first-class packet containing:

a) **Appointment Reminder Letter** that includes:

- Date and time of the appointment, with CC phone number and contact to call if the participant has questions.
- Location of CC.
- Approximately how long the appointment will take.
- Information about the contents of the mailed packet.
- Request to bring her study pill bottles (empty or not) and pill organizer to the CC (HRT, CaD).
- Request to bring her completed *Form 53 - HRT Calendar* (HRT participants with a uterus at the first semi-annual visit only).
- Request to complete and bring in mailed forms, as appropriate.

b) **Self-Administered Forms**, which may include:

- *WHIP 0441 - Personal Information Update (*see *Section 16.1.2.1 - Introduction and Personal Information Update* and *Section 16.3.3.6 - Personal Information Update).*
- *Form 33 - Medical History Update.*

c) **Other Materials**, such as:

- WHI logo bag for her to return study pills (HRT, CaD).
- Map to the CC and parking validation, as appropriate.

16.2.1.2 Two days Before a Semi-Annual Visit

Prepare ahead for semi-annual visits scheduled in the next few days:

- Ensure a current visit plan, appropriate forms, and participant labels are in each participant's file, including your CC's semi-annual contact checklist.
- Make a phone call to the participant to remind her of the appointment and items she should bring with her.

16.2.2 Conducting the Semi-Annual Visit (Required)

Each CC can organize the flow of the visit to fit its needs as long as the flow meets the following requirements:

- For HRT participants collect study pills and assess adherence, complete *Form 10 - HRT Management and Safety Interview* and collect *Form 53 - HRT Calendar* (HRT participants with a uterus at the first semi-annual visit only) **before** dispensing additional study pills. Note that *Form 10* should be completed at the next **two** routinely scheduled visits or contacts after stopping HRT intervention (see *Section 16.7.1 - Participants Who Have Stopped Intervention*).
- For CaD participants (at SAV2 and beyond), assess study pill adherence and *complete Form 17 - CaD Management and Safety Interview* **before** dispensing additional CaD study pills. CaD participants can choose to switch to the other study pill formulation at each contact. Note that *Form 17* should be completed at the next routinely scheduled visit or contact after stopping CaD intervention (see *Section 16.7.1 – Participants Who Have Stopped Intervention*).
- For HRT and/or CaD participants, refer to the CP any appropriate participant questions, concerns, or information about medical events that might necessitate discontinuing study pills (see *Section 5 - HRT, and/or Section 7 - CaD*). The CP will help evaluate and clear the participant before dispensing additional study pills. If you dispense study pills at the semi-annual contact, dispense only a 6-month supply (see *Section 16.2.2.e - Dispense Study Pills*).
- It is strongly recommended that staff remain blinded to a DM participant's treatment arm. See *Section 4 - Screening*.

16.2.2.1 Reception

When the participant arrives for her semi-annual visit, have her check in with the receptionist. The receptionist should:

- Warmly greet the participant by name and welcome her back to the CC.
- Ask the participant if she has brought her completed forms and study pill bottles (empty or not) and pill organizers as appropriate. Collect and attach the returned forms to the top of her participant file. If she has not remembered the forms, provide her with a replacement set and ask her to complete them while she is waiting.

- State the approximate time needed to complete the visit and explain the visit flow.
- Indicate a comfortable place in the reception area where the participant may wait.
- Notify the clinic staff that the participant is waiting.

Try to limit participant's wait to no more than 10 minutes before she is seen by an interviewer.

The participant's spouse or household members may accompany her to the interview room. If household members are also participants, they must complete separate forms and have separate interviews.

16.2.2.2 Semi-Annual Visit Procedures (Required)

a) Obtain General Medical Releases

Ask the participant to sign several new copies of your CC's *General Medical Release Form* (see model in *Vol. 2, Appendix E.5.1*). Explain to the participant that these new forms will replace the last ones she signed. Many institutions require a signed release within the last 3 to 6 months before releasing any information. Having a recently-signed General Medical Release will simplify future collection of outcome documents.

b) Review Appropriate Forms

Review with the participant the appropriate required forms, as indicated in *Vol. 1 - Study Protocol and Policies, Table 1-A1.2 - Frequency of Collection*. This form review, in general, should take approximately 30 seconds (see *Vol. 2 – Procedures, Sec. 18.2.3—Review of Forms*). Identify missing pages and remind the participant to complete them. If the participant indicates she has had any events or conditions on *Form 33 - Medical History Update* that necessitate more detailed information for an outcomes investigation, ask her to complete *Form 33D - Medical History Update (Detail)* (see *Form 33* instructions for the algorithm that triggers a *Form 33D* and *Vol. 8 - Outcomes, Section 2 - Ascertainment*).

c) Assess Adherence to Study Pills (HRT, CaD)

Assess the participant's adherence to taking the study pills (this may be an actual or estimated adherence collection.) (See *Section 15.6 - Study Pill Adherence Monitoring*.) Estimate what her adherence has been, and record this on *Form 10* or *Form 17*. Do not let the participant know that you are assessing pill adherence.

d) Complete HRT and/or CaD Management Safety Interview (HRT, CaD)

Complete *Form 10 - HRT Management and Safety Interview* and/or *Form 17 - CaD Management and Safety Interview*, using the script on the form. Each CC can decide on the appropriate staff to conduct this interview, but the staff must be appropriately trained and certified. Interviewers must refer decisions about possible serious conditions or concerns to the CP as soon as possible. Adherence concerns should be addressed or referred to the retention specialist, as appropriate. See *Section 16.1.2.2 – Safety Interview* for guidelines.

e) Dispense Study Pills (HRT, CaD)

If a participant has no findings on *Form 10, Form 17*, other forms, or reports that contraindicate her continuing on study pills (see *Section 5 - HRT* and/or *Section 7 - CaD*), dispense new study pills (if she is to receive a new six-month supply.)

- Follow the procedures described in *Section 15.4 - Medication Dispensing* (note the participant's preference for CaD study pill formulation).
- Inform the participant that you will be giving her a new bottle of study pills and that you will be keeping her old study pills that were dispensed at the last CC visit.
- Offer her a new *HRT Handbook* and/or *CaD Handbook* and review the pill instructions with her.

- Offer her a new pill organizer. (She may benefit from two pill organizers if she takes multiple other pills or needs to track the twice daily dosing of CaD separately).
- Remind the participant to call the CC if she develops new symptoms or concerns with the study pills, loses her study pill bottle, or knows she is going to run out of study pills before her next visit.
- Remind her to bring all her study pill bottles (empty or not) to each routine clinic visit.

For HRT participants, only a 6-month supply of HRT study pills can be dispensed at randomization and at the first semi-annual visit (SAV1). At AV1 and subsequent annual visits, a 12-month supply of HRT study pills can be dispensed (after all required tasks are completed and safety considerations reviewed).

For CaD participants, only a 6-month supply of CaD study pills can be dispensed at AV1 and SAV2 (to ensure that the participant tolerates the formulation she has chosen). Do not dispense any more than a 6-month supply of a particular form of CaD - chewable or swallowable - until the participant has tolerated at least a full-year's worth of that formulation. After a participant has been on one formulation for a full year, a 12-month supply of CaD may be dispensed at annual visits thereafter.

NOTE*:* At semi-annual visits or contacts, you may only dispense a six-month supply of study pills (HRT or CaD). At annual visits you may dispense a six-month or twelve-month supply of pills, as appropriate.

16.2.3 Exit Interview

After completing required procedures and forms, review the semi-annual visit checklist and visit plan to be sure you have completed all required activities or have recorded the reason an activity is not completed. Spend a few minutes talking with the participant to maintain rapport and discuss her further adherence and interest in the study. Record any concerns and how you addressed them in the participant's contact notes. Make sure the participant is aware that:

- Her contribution to WHI is invaluable.
- The CC staff are interested in her safety and her activities with the study.
- She should contact the CC any time she might have questions or concerns.

Schedule an appointment for the next annual visit within the appropriate window (± 2 weeks around the annual visit target date). Explain to the participant that two weeks before the visit she will receive a packet in the mail containing a reminder letter, forms for her to complete, and other appropriate materials (see *Section 16.3.1.2 - Two Weeks Before the Annual (CT) and Third-Year (OS) Visit*).

Inform her of other appropriate annual visit activities, based on her annual visit plan. Relevant activities that might be scheduled and should be mentioned are described in *Section 16.3 - Annual (CT) and Third-Year (OS) Visit (Required).*

Make sure the participant leaves with the following materials:

- *Form 53 - HRT Calendar* (HRT participants with a uterus at the first semi-annual visit only).
- HRT study pills (HRT) - 6-month supply, as appropriate.
- CaD study pills (CaD) - 6-month supply, as appropriate.
- *HRT Handbook* and/or *CaD Handbook*, if needed (HRT, CaD).
- Appointment card with date for next annual visit and other relevant information about scheduled activities.

Participant retention may be promoted by also sending a personalized thank-you card within a week of the contact.

16.3 Annual (CT) and Third-Year (OS) Visit (Required)

Clinic visits are conducted annually for all CT participants and for OS participants in the third year. The activities of the annual visit will vary according to the trial component. See *Vol. 1 - Study Protocol and Policies, Table 1-A1.2 - Frequency of Collection* for the schedule of activities per contact. The target date for the annual visits is the anniversary of the randomization date for CT and the third anniversary of the enrollment date for OS. The standard window for CT annual visits and OS Year 3 visits is +/- 3 months around the target date for the contact. Selected tasks such as CT Pap, pelvic exams, and mammograms have wider windows. The time limits for collecting tasks are given in *Table 16.1* (see also *Section 16.4.1.2 - Strategies for Managing Missed Contacts*) *WHIP1445 - Task Completeness* uses these windows in its parameters for Standard and Expanded windows.

The purpose of the annual (CT) and third-year (OS) visit is to:

- Promote rapport with the participant and foster her continued interest in the study.
- Collect updated contact and medical information, including information on potential outcomes.
- Obtain current signatures on release of medical records forms.
- Collect information on symptoms and other concerns (HRT, CaD).
- Assess and promote study pill adherence and dispense a new supply of study pills (HRT, CaD).
- Collect interim measurements.
- Schedule the next routine visit (CT).

16.3.1 Preparation for the Annual (CT) and Third-Year (OS) Visit

Print out an annual visit plan report (*WHIP 0144 - Tasks Required at Visit*) for the participant. This will list all the required WHI activities for that visit, including any subsample activities for which the participant has been selected. Run a preliminary CaD eligibility determination before the first annual visit for CT participants to indicate if an invitation to join the CaD trial should be offered. Clinical Centers are required to offer CaD at AV1, however, CaD may also be offered at any time through AV2. Use of an annual visit checklist that lists all WHI-required and CC-specific annual visit activities is recommended (see model *in Vol. 2, Appendix E.4.7 - Model Annual (CT) or Third-Year (OS) Visit Checklist*). Designate one person to review the checklist before the participant leaves the CC to be sure you have completed all the activities.

16.3.1.1 Two Months Before the Annual Visit (CT)

Approximately two months before the scheduled annual visit, take the following steps to obtain appropriate reports on the CT participant:

- **Obtain Mammogram Results (annually for HRT, every other year for DM)**

  Schedule a mammogram at an accredited facility for the participant. If the participant is having mammograms through her own physician or clinic, call her to see if she has had her annual mammogram. If she has not yet had her mammogram, ask her to schedule it and call the CC with the date she is to have the test. If the participant has had her mammogram, write or call for the results. Refer to *Section 12 - Mammography*.

  The CP should review the mammogram report when it arrives at the CC. Record the appropriate information on *Form 85 - Mammogram*. If a repeat mammogram is recommended in less than one year, record this information on *Form 85 - Mammogram.*

The following two reports may be helpful for tracking follow-up mammograms:

- *WHIP 0476 - Mammograms Requiring 6-Month Follow-Up* - lists all participants who have "probably benign findings" on *Form 85* and no follow-up results entered on that same *Form 85*.

- *WHIP 1227 - Referral Follow-Up* - lists women who had abnormal results and/or required follow-up for a given procedure, such as *Form 85 - Mammogram*.

- **Obtain Pap Smear Results (HRT participants with a uterus in years 3, 6, and 9 if performed by personal physician)**

  If a participant chooses to have her personal physician obtain her Pap smear, ask her to have a copy of the lab report sent to the CC. The CP should review the Pap smear reports when they arrive at the CC. Record the appropriate information on *Form 92 - Pap Smear*. Some participants may also insist that their pelvic exams be performed by their personal physician. Reports of these exams should also be obtained (a written report or a verbal report by a clinician is required in years 3, 6, and 9).

16.3.1.2 Two Weeks Before the Annual (CT) and Third-Year (OS) Visit

Two weeks before the annual visit, mail the participant a first-class packet containing:

a) **Appointment Reminder Letter** that includes:

- Date and time of the appointment, with CC phone number and contact to call if the participant has questions.
- Location of CC.
- Approximately how long the appointment will take.
- Information about the contents of the mailed packet.
- Information about joining the CaD trial (eligible CT participants).
- Request to bring all her study pill bottles (empty or not) and weekly pill organizer(s) to the CC (HRT, CaD).
- Request to bring her completed *Form 53 - HRT Calendar* (HRT participants with a uterus at the first annual visit only).
- Request to complete and bring in mailed forms, as appropriate.
- Request to wear light, two-piece clothing for measurements.
- Request not to eat or drink anything but water for 12 hours before her visit if she is to have a fasting blood draw. She should not smoke one hour before her visit nor engage in vigorous exercise eight hours before her visit. She should take any regularly-scheduled medications before her visit, **except** medications for diabetes (she should bring these to the visit to take after her blood draw, unless her primary physician has instructed her otherwise) (Years 1, 3, 6, 9 in CT; year 3 in OS).
- Notification of endometrial subsample participant (Years 3, 6, 9). Pathology results from an aspiration or D & C may be substituted if done during the previous 12 months.
- Notification of 4DFR subsample participant (Year 1 only in DM). See *Section 10.1.3 Follow-up Visit Record Completion*.
- Request to bring in all of her current prescription and over-the-counter medications and supplements (Years 1, 3, 6, 9 in CT; Year 3 in OS).
- Information about other activities that will take place during the visit.

b) **Self-Administered Forms**, which may include (depending on the visit plan):

- *Form 33 - Medical History Update*.
- *WHIP 0441 - Personal Information Update*.
- *Form 35 - Personal Habits Update* (Years 1, 3, 6, 9 in CT).
- *Form 38 - Daily Life* (if needed).
- *Form 60 - Food Frequency Questionnaire* and *Form 61 - How to Fill Out the Food Questionnaire* (DM, OS - if needed).
- *Form 62 - Four-Day Food Record* (assign dates for completion on her form) and *Form 69 - Keeping Track of What You Eat* (DM - if needed).
- *Form 143 - OS Follow-Up* (Year 3 in OS).

c) **Other Materials**

- WHI logo bag (for participant to bring her study pills and bottles, current medications, and current supplements, as appropriate, to the CC).
- #2 pencil for completing any mark-sense forms included in the packet.
- Map to the CC, if appropriate.
- *Invitation to Join CaD* and CaD consent (eligible CT participants).
- At Bone Density sites, include a 30 ml urine container labeled with the participant's ID label and a copy of a Urine Home Collection instruction sheet. (See *Section 11.5.3 - Preparation Before the Visit*).

Check that *Form 85 - Mammogram* has been completed (CT participants, as appropriate). If not, take steps to get the results and enter them on the form.

16.3.1.3 A Few Days Before the Annual (CT) and Third-Year (OS) Visit

Prepare ahead for the annual visits scheduled in the next few days:

- Ensure a current annual visit plan (*WHIP 0144 - Tasks Required at Visit*), appropriate forms, and participant labels are in each participant's file, including the annual visit checklist.
- Check the participant's file to be sure you have received appropriate reports.
- Make a phone call to the participant to remind her of the appointment and items she should bring with her.
- Ensure Dietary Assessment staff are available to document *Form 62 - Four Day Food Record*, if needed (DM subsample in Year 1).

16.3.1.4 Activities on the Morning of the Annual (CT) and Third-Year (OS) Visit

Each day prepare for the annual exams scheduled for that day:

- Prepare supplies for blood draws, if needed.
- If there are gynecological exams scheduled for that day, set up appropriate equipment (see *Section 4.3.3.3 - Activities on the Morning of SV2*).
- Check that the ECG machine is stocked with paper, has adequate memory space, and all additional necessary equipment is present (Years 3, 6, 9).

16.3.2 Conducting the Annual (CT) and Third-Year (OS) Visit (Required)

Each CC can organize the flow of the visit to fit its needs as long as the flow meets the following requirements:

- Perform the blood pressure measurement before the blood draw (or at least one-half hour after in the opposite arm) and other stressful tests such as ECG, pelvic exam, endometrial aspiration, and mammogram.
- Assess HRT and CaD study pill adherence before completing *Form 10 - HRT Management and Safety Interview* and *Form 17 - CaD Management and Safety Interview.*
- Review the mammogram report before dispensing HRT study pills. Mammograms not scheduled and/or mammogram reports not available by the annual visit need not hold up dispensation of a six-month supply of HRT study pills (a 12-month supply cannot be dispensed if the mammogram report is not available). The mammogram must be scheduled and a report obtained before the next semi-annual contact in order to dispense an additional six-month supply of HRT study pills.
- Review *Form 53 - HRT Calendar* before dispensing HRT study pills (HRT participants with a uterus at the first annual visit).
- Complete *Form 10 - HRT Management and Safety Interview* before dispensing HRT study pills.
- Complete *Form 17 - CaD Management and Safety Interview* before dispensing CaD study pills.
- Refer questions of concern as soon as possible to CP for evaluation and clearance before dispensing HRT or CaD study pills.

16.3.2.1 CaD Review at Annual Visit (Required)

Determine if the participant is eligible and interested in the CaD component of the CT. See *Section 7 - Calcium and Vitamin D Intervention*. CaD screening and randomization procedures include:

- Running a preliminary CaD eligibility determination (Task ID 930).
- Offering a "taste test" of a CaD study pill formulations (see *Section 7.1.4.1 - CaD Study Pill Taste/Swallow Test).*
- Administering *Form 16 - Calcium/Vitamin D Eligibility Assessment*.
- Reviewing the CaD consent form with appropriate participants.
- Completing *Form 11 - Consent Status*, Task 15 - CaD Consent as needed.
- Running a final CaD eligibility determination and then randomizing the participant to CaD.

16.3.2.2 Reception

When the CT or OS participant arrives for her visit, have her check in with the receptionist. The receptionist should:

- Warmly greet the participant by name and welcome her back to the CC.
- State the approximate time needed to complete the visit and explain the visit flow.
- Ask the participant if she has brought her completed forms and study pill bottles (empty or not) and pill organizers, as appropriate. Collect and attach the returned forms to the top of her participant file. If she has not remembered the forms, provide her with a replacement set and ask her to complete them while she is waiting.
- Indicate a comfortable place in the reception area where the participant may wait.
- Notify the clinical staff that the participant is waiting.

Try to limit the participant's wait to no more than 10 minutes before she is seen by an interviewer.

The participant's spouse or household members may accompany her to the interview room. If household members are also participants, they must complete separate forms and have separate interviews.

16.3.2.3 Annual (CT) and Third-Year (OS) Visit Procedures (Required)

a) Obtain General Medical Releases

Ask the participant to sign several new copies of your CC's General Medical Release form (see model in *Vol. 2, Appendix E.5.1*) Explain to the participant that these new forms will replace the last ones she signed. Many institutions require a signed release within the last 3 to 6 months before releasing any information. Having a recently-signed General Medical Release will simplify future collection of outcome documents.

b) Review of Self-Administered Forms

Review the appropriate self-administered forms, as indicated in *Vol. 1 - Study Protocol and Policies, Table 1-A1.2 - Frequency of Collection.* Go over each form for completeness. This form review should take approximately 1 minute (see *Vol. 2 – Procedures, Sec. 18.2.3–Review of Forms*). Identify missing pages and remind the participant to complete them. If the participant indicates she has had any events or conditions on *Form 33 - Medical History Update* that necessitate more detailed information on potential outcomes, ask her to complete *a Form 33D - Medical History Update (Detail)* (see *Form 33* instructions for the algorithm that triggers a *Form 33D* and *Vol. 8 - Outcomes, Section 2 – Ascertainment*).

c) CaD Information and Consent (eligible CT participants)

Provide women interested in CaD with a detailed in-depth description of the trial. Provide the participant with an information-sharing session and an opportunity for her to ask questions. Offer her a taste and/or swallow test of the CaD pill formulations, and review and sign the CaD consent. See *Section 7.1.4.1 - CaD Study Pill Taste/Swallow Test*, informed consent, and randomization procedures.

d) Collect Blood Sample (CT at year 1 and subsample in Years 3, 6, and 9; OS at Year 3)

If the participant is designated to have a blood sample collected at this annual visit, direct her to the phlebotomy area and follow guidelines in *Section 11 - Blood and Urine Collection, Processing and Shipment* regarding specimen collection. Participants in HRT may need a specimen sent to the local lab for triglyceride analysis, if the serum appears lipemic. Participants in OS need a specimen sent to the local lab for analysis of hematocrit, white blood count (WBC) and platelet count (or CBC if more convenient) as well as the routine samples to send to McKesson.

Note: All CT and OS participants are required to be fasting at least 12 hours to have their blood drawn.

e) Collect Urine Sample (Bone Density Sites only: CT in Years 1, 3, 6, and 9; and OS in Years 3 and 9)

Collect the urine sample from appropriate CT and OS participants. Process the urine sample as described in *Section 11.5.4 - At the Visit.*

f) Assess Adherence to Study Pills (HRT, CaD)

Assess the participant's adherence to taking the study pills. Be sure to include study pills she may have in a pill organizer. Even if the participant forgot to bring her study pills, you are required to enter an estimated pill count into WHILMA. If your adherence collection is an estimate, give the participant a mailer and ask her to mail her study pills to the CC. (*See Section 15.6 - Medication Adherence Assessment* for procedure.) This task must be done before completing the safety interviews and

dispensing study pills. Do not let the participant know that you are assessing pill adherence. If adherence to study pills is < 80% adherence problems are anticipated. Evaluate whether the participant should be referred to the Intensive Adherence Program (see *Section 15.8 - Intensive Adherence Program* for assistance). For CaD participants, determine if adherence problems may be due to the particular formulation she is taking, and consider switching to the other form at this visit.

g) Complete HRT and/or CaD Management and Safety Interview (HRT/CaD)

Complete *Form 10 - HRT Management and Safety Interview* and/or *Form 17 - CaD Management and Safety Interview*, using the script on the form. Each CC can decide on the appropriate staff to conduct this interview, but the staff must be appropriately trained and certified. Interviewers must refer decisions about possible serious conditions or concerns to the CP as soon as possible. Adherence concerns should be addressed or referred to the retention specialist, as appropriate. See *Section 16.1.2.2* for safety interview guidelines, and *Section 16.7.1* for procedures on completing *Form 10* and *Form 17* when participants stop the intervention.

h) Complete *Form 39 - Cognitive Assessment* (HRT participants 65 years or older at baseline and in years 1, 3, 6, and 9)

Complete the cognitive assessment interview using *Form 39 - Cognitive Assessment*. See *Section 9.11 - Cognitive Assessment* for details.

i) Review Mammogram Report (HRT annually; DM every other year)

Pull the radiologist's mammogram report from the participant's file and review it with her. Explain any terms that might be unfamiliar and answer any questions that she might have. Make referrals, if appropriate. See *Section 12 - Mammography* for guidelines. Mammograms not scheduled and/or available by the annual visit need not hold up dispensation of a six-month supply of HRT study pills. However, the mammogram must be scheduled and a report obtained before the next semi-annual contact in order to dispense an additional six-month supply of HRT study pills.

j) Enter Current Medications and Current Supplements (CT in Years 1, 3, 6, and 9; OS in Year 3)

Ask the participant for all current medications and vitamin/mineral supplements she brought with her. Remind the participant that only supplements taken at least once a week and medications used at least twice a week for the past two weeks will be entered. Enter the medications and supplements into the database (see *Section 4.2.4.6 - Current Medications and Current Supplements Inventory Review* and *Vol. 5 - Data System, Section 7.3 - Direct Data Entry*). Do not enter any WHI open label medications into the current medications inventory. If the HRT participant is taking any hormones (e.g., estrogen, progesterone, tamoxifen, or testosterone), refer her to the CP. The CP may need to communicate with her primary care provider regarding the HRT participant's hormone use.

k) Perform Physical Measurements (CT at year 1 and subsample in Years 3, 6, and 9; OS in Year 3)

Obtain physical measurements of resting pulse, blood pressure, weight, height, (CT annually; OS in Year 3). Obtain height and weight at BD CCs at OS AV6. Obtain waist and hip circumferences (CT in Year 1 and subsample of CT in Years 3, 6 and 9; OS in Year 3). At all other annual visits, leave the hip and waist measurements blank on *Form 80 – Physical Measurements*.

Record results of all physical measurements on *Form 80 - Physical Measurements*. See *Section 9 - Clinical Measurements, 9.1* through *9.5* for guidelines for performing these measurements.

l) Perform Functional Status Measurements (CT subsample in Years 1, 3, 6, and 9)

Obtain functional status measurements of grip strength, chair stand, and timed walk and record results on *Form 90 - Functional Status*. See *Section 9.6 - Functional Status Measurements* for guidelines for performing these measurements.

m) Complete ECG (CT in Years 3, 6, and 9)

Perform an ECG if this is the appropriate year for the CT participant and complete *Form 86 - ECG*. See *Section 13 - ECG Procedures* for guidelines for performing this procedure.

n) Perform Clinical Breast Exam (CBE) (HRT annually, optional for DM participants who have not consented to annual CBE)

Perform a CBE on appropriate CT participants and complete *Form 84 - Clinical Breast Exam*. See *Section 9.7.2 - Performing the Clinical Breast Exam* for a complete description of the procedure. A participant may also review the breast self-exam video if she wishes.

o) Perform Pelvic Exam Annually and Pap Smear in Years 3, 6, and 9 (HRT participants with a uterus)

With the stopping of E+P in tervention on July 9, 2002, pelvic examinations and Pap smears for E+P participants are no longer required, but may be continued for retention purposes, at CC option. When considering this option, keep in mind that these examinations were included in the E+P consent and serve as a retention tool for many participants. CCs should document any examinations that do take place in the CC on the appropriate forms. If an E-plus-P participant prefers to have her future exams done by an outside provider, you are not required to obtain outside provider reports.

Perform a pelvic exam and Pap smear on appropriate HRT participants and complete *Form 81 - Pelvic Exam* and *Form 92 - Pap Smear*. See *Section 9.9.2 - Performing the Pelvic Exam and Obtaining the Pap Smear*.

p) Perform an Endometrial Aspiration (subsample of HRT participants with a uterus in Years 3, 6, and 9)

The routine 6% subsample endometrial aspirations are discontinued with the stopping of E+P intervention on July 9, 2002.

Perform an endometrial aspiration on appropriate HRT participants and complete *Form 82 - Endometrial Aspiration*. Follow the guidelines in *Section 9.10.2 - Performing the Endometrial Aspiration*. If an identified EA subsample participant has had an endometrial aspiration or D & C during the past 12 months, those results may be used to fulfill her subsample requirement. If a participant is in the designated EA subsample and the clinician is unable to gain entry into the uterus (or the participant refuses the EA), a transvaginal ultrasound is required.

q) Document Four-Day Food Record (DM subsample in Year 1)

If the participant is in the designated subsample to complete a 4DFR, a certified dietary assessment staff person must document the 4DFR. See *Section 10.1.5 - Follow-Up Visit Food Record Documentation*.

r) Dispense Study Pills (HRT, CaD)

If a participant has no findings on the safety interview, physical exam, or test results available that contraindicate her continuing on study pills (see *Section 5 - HRT and Section 7 - CaD*), dispense new study pills (a six-month or twelve-month supply, as appropriate):

- Follow the procedures described in *Section 15.4 - Medication Dispensing* (note participant's preference for CaD study pill formulation). Inform the participant that you will be giving her a new bottle of study pills and that you will be keeping her old study pills that were dispensed at the last CC visit.
- Offer her a new *HRT Handbook* and/or *CaD Handbook* and review the pill instructions with her.
- Offer her a new pill organizer, if needed.

- Remind the participant to call the CC if she develops new symptoms or concerns with the study pills, loses her study pill bottle, or knows she is going to run out of study pills before her next visit.
- Remind her to bring her study pill bottles (empty or not) each subsequent visit.

s) Schedule Bone Densitometry (Bone Density Sites: CT in years 1, 3, 6, and 9; OS in years 3, 6, 9)

Schedule and perform a bone densitometry and complete *Form 87 - Bone Density Scan*. If the densitometry cannot be performed by the time of the follow-up visit, schedule the measurement as soon as possible.

t) Complete *Form 33 – Medical History Update* and OS Follow-up Forms (Bone Density Sites: OS in years 3, 6, 9)

The CCC does not mail forms to OS participants at bone density sites during years 3, 6, and 9, so these forms (*Form 33 – Medical History Update* and either *Form 143, 146,* or *Form 149 – OS Follow-up Questionnaire*) must be collected at the clinic visit.

16.3.2.4 Exit Interview

After completing the procedures and forms, review the annual visit checklist and visit plan to be sure you have completed all WHI-required and CC-specific annual visit activities or have recorded the reason an activity is not completed. Forward all forms to data-entry. Spend a few minutes with the participant to maintain rapport and discuss her further adherence and interest in the study. Record any concerns the participant may have and how you addressed them in the participant's contact notes. Make sure the participant is aware that:

- Her contribution to WHI is invaluable.
- The CC staff are interested in her safety and her activities with the study.
- She should contact the CC any time she might have questions or concerns.

Schedule an appointment for the CT participant's next semi-annual visit within the appropriate window (± 2 weeks) or remind her of the target date for a semi-annual contact. Explain to the participant that she will receive a packet of appropriate materials approximately 2 weeks before the target date and discuss appropriate semi-annual contact procedures and forms with her (see *Section 16.2 - Semi-Annual Contact (CT only) (Required*)).

Make sure the participant leaves with all the materials you have given her. These may include:

- HRT study pills (HRT).
- CaD study pills (CaD).
- New pill organizer(s), if appropriate (HRT/CaD).
- *HRT Handbook* and/or *CaD Handbook (*HRT, CaD).
- Appropriate study-wide annual retention item.
- Appointment card with date for the next semi-annual contact and estimated time needed to complete the semi-annual contact activities (if appropriate).

Participant retention may be promoted by sending a personalized thank-you card within a week of the visit.

16.3.3 Post-Visit Review (Required)

Review appropriate lab, pathology, and other reports that arrive after the annual visit. It is recommended that you provide the participant with these findings and required that you follow appropriate alert procedures if critical values are obtained (see *Vol. 1, Section 1 - Study Protocol and Procedures*).

Specific reports may indicate that HRT study pills should be discontinued either temporarily (pending further work-up) or permanently, even if pills were dispensed at the annual visit (see *Section 5.5.3 – Health Problems That May Require Temporary Discontinuation* and *Section 5.5.4 – Health Problems Requiring HRT*

Termination). Note that rules for stopping CaD study pills are not based on reports obtained from annual visit tests. To discontinue HRT study pills after the annual visit, follow the steps below.

- Call the participant with the results (this call must be made by a CC physician or CP, preferably the one who did the exam). Refer the participant to her primary physician. If any findings are suspicious for cancer, the CC physician or CP must call the participant's primary physician (with the participant's consent).
- Send copies of all pertinent reports to the participant's primary physician (with the participant's consent).
- Ask the participant to return her unused HRT study pills. Send a stamped, self-addressed envelope for her to return the study pills to the CC. Enter adherence information into WHILMA (obtain an estimated count at the time of the contact and then enter an actual count when you receive the study pill bottle).
- Instruct the participant to call the CC if the problem is investigated. If found not to be a safety concern, she may be eligible to resume taking HRT study pills.
- Complete a *Form 7 - Participation Status* and/or a *Form 54 - Change of Medications*, as appropriate.

16.3.3.1 Blood Test Results (Required)

Review lab results when returned by the local laboratory if blood was drawn. Follow procedures outlined in *Section 4.2.7.1 - Blood Analysis Results*.

16.3.3.2 Pelvic Exam and Pap Smear Results (HRT) (Required)

Review the pelvic exam and/or Pap smear results when they come in, as appropriate. Complete the remainder of *Form 81- Pelvic Exam* and/or *Form 92 - Pap Smear*. See *Sections 5.4 - Managing Symptoms* and *5.5 - Major Health Problems* for referral information.

16.3.3.3 Endometrial Aspiration Results (HRT) (Required)

Review the pathology results of the aspiration and complete the remainder of *Form 82 - Endometrial Aspiration*. Request slides from the local lab to send to McKesson for central pathology review. (See *Section 5.7 – Endometrial Aspiration Pathological Review.*)

16.3.3.4 Mammogram Report Results (Required)

Review mammogram reports for those mammograms scheduled between the annual and next semi-annual visit and document findings on *Form 85 - Mammogram*. Refer all abnormal findings to the participant's primary physician.

16.3.3.5 Bone Density Scan (Bone Density Sites only) (Required)

Confirm that the bone density scan was completed and complete the remainder of *Form 87 - Bone Density Scan.*

16.3.3.6 Personal Information Update (*WHIP 0441*)

Changes in a participant's address, phone number and contacts should be key-entered into the Members block in WHILMA (see *Volume 5, Section 5.1.2 – Entering a New Participant*). Changes to the alternate contacts that are listed on this report should be key-entered into the original *Form 20 – Personal Information* that was entered in WHILMA at baseline for the participant (See *Volume 5, Section 7.1.3 – Making Corrections to Key-entered Data).* Do not enter a new *Form 20.*

An item to collect the participant's father's last name" was added to *Form 20* with version 37 of WHILMA. This item will be added to the Personal Information Update report for Version 38 of WHILMA. You can inform the participant that this information will be kept confidential and helps the WHI staff stay in contact

with her. For participants who completed their baseline *Form 20* before the publication of version 37 of WHILMA, you will need to key-enter the "Father's Last Name" into WHILMA after it is collected on the Personal Information Update.

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16.4 Follow-Up Contact Problems for Annual (CT) and Third-Year (OS) Visits

There may be many different reasons why participants might miss a scheduled contact, including:

- Transportation difficulties
- Illness
- Personal stress or life events
- Vacations and travel
- Temporary or permanent moves
- Decreased interest in or dissatisfaction with WHI

Strategies for managing follow-up contact problems for annual (CT) and third-year (OS) visits are detailed in the sections below. Strategies for managing annual mailed contacts in OS are described in *Section 16.5 - OS Annual Mail Contact and Follow-Up of Non-Responders*.

16.4.1 Missed Follow-Up Contacts

16.4.1.1 Strategies for Avoiding Missed Contacts

Strategies for avoiding missed follow-up contacts depend on the type of contact and the participant's availability and willingness to participate. Clinical Centers can refer to *Table 16.3 – Options for WHI Task Completion* for the available options for collecting the critical tasks for each study component.

- **If you are unable to complete a phone contact**, make several attempts to contact the participant at various times and days. Each CC should decide, based on their resources and experience, how many phone call attempts to make for any one participant. If you are unable to contact the participant by phone after several attempts, try to make initial contact by mail using a postcard that asks for current contact information and offers a phone number and CC staff person name for the participant to call with any questions. If you are still unable to contact the participant, begin efforts to locate her. Use *Form 23 - Search to Locate Lost Participant* to record your attempts to locate the participant (*see Section 17.3 - Locating "Hard to Find" Participants*). Although participants can miss the early phone call and still remain active in HRT or CaD, such contacts have been shown in other clinical trials to be critical for promoting ongoing adherence and retention.

- **If the participant cancels a scheduled visit** or fails to show up, reschedule her visit as soon as possible.

- **If the participant is reluctant to complete a required visit** (i.e., annual visits in CT and the semi-annual visit one in HRT, discuss the importance of this visit for safety, getting updated health information, and dispensing additional study pills, as appropriate. Appropriate CC staff should discuss with the participant (and help to resolve) any barriers to making a clinic visit (see *Section 17 - Retention*).

- **If the participant refuses a visit** (whether required or not), attempt to complete the contact as much as possible by mail and/or phone, as appropriate (a phone interview is needed to complete *Form 10 - HRT Management and Safety Interview* or *Form 17 - CaD Management and Safety Interview*). The safety interviews must be completed for HRT and CaD participants before dispensing additional study pills. Initiate a *Form 24 - Retention Worksheet* and refer to appropriate CC staff (see *Section 17 - Retention*), as needed.

- **If the participant refuses any routine contact**, determine her willingness to continue with the intervention and/or follow-up. Appropriate CC staff should discuss with the participant (and help to resolve) any barriers to making a clinic visit (see *Section 17 - Retention*). If she is not willing to continue with the intervention and/or with full follow-up procedures, complete *Form 7 - Participation Status*.

16.4.1.2 Strategies for Managing Missed Contacts (Required)

In general, every effort should be made to get participants who miss a follow-up contact back on their routine schedule. Specifically, if a follow-up contact is missed, the next scheduled contact should be planned such that:

- Missed annual visit tasks are conducted, even if the next scheduled contact is a semi-annual contact (CT).
- Missed year 1, 3, 6, or 9 visit tasks are conducted, even if the next scheduled contact is a year 2, 4, 5, 7, or 8 visit (CT)
- Missed third-year OS visit tasks are conducted up to 15 months after the target third-year date (OS).

In March 2000, the Steering Committee defined the allowable window for collection of data. In general, the time limits extend from several months before the target date for a task up to the window for the next target date. For **CT**, the general time limits are:

- Tasks due every 6 months: -/+3 months
- Tasks due at every 12 months: -/+6 months
- Tasks due less frequently than every 12 months: -6/up to 6 months before the text target date
- Tasks collected only once in follow-up -6/+30

For **OS**, the general time limits are:

- Tasks due for Year 3 Visit: -6/+15 months
- Tasks due for other Annual Contacts: -2/+10 months
- Bone Density tasks: -3/+15 months

The exact time limits for each task is given in *Table 16.1 - Time Limits for Collecting Tasks* (the same table is presented in the Outlook Public Folders under Manual Information). The table gives CT time limits of tasks on page 1 and OS time limits on page 2. The footnotes, described on the bottom of the second page, are similar to the foot notes in Appendix 1-A1 in the protocol. Note that the time limits listed in the table correspond to the "expanded" windows used by *WHIP1445-Task Completeness*. For CT, the "Subsample" column gives the percentage of participants on whom the task is collected.

Initiate a *Form 24 - Retention Worksheet* (recommended) for participants who are not willing to continue follow-up visits (see *Section 17 - Retention*). If follow-up visits have been missed and the participant's status has changed on *Form 7 - Participation Status*, follow reactivation procedures for the next follow-up visit (see *Section 17.4.5 - Reactivation of Participants with Changes in Participation Status*).

16.4.2 Minimum Procedures Required for a CT Participant to Remain on Intervention (Required)

Although appropriate and complete data collection are critical to the success of WHI, there may be situations in which full data collection at a routine contact is not possible. Minimum requirements for routine contacts, if the participant is unable or unwilling to complete all activities, vary by trial component and are based primarily on safety concerns.

Note that if the semi-annual *Form 33 - Medical History Update* is **not** administered, the next annual visit *Form 33* must show the date of the previous annual visit *Form 33* as the "date of last medical history update" (see appropriate forms instructions).

If a woman completes the minimum requirements listed below, she may continue on intervention even if she no longer attends CC visits and/or can no longer communicate (as long as a proxy respondent answers for her).

Table 16.1
Time Limits for Collecting Tasks
CT

Task	Name	SAVs*	Window**	AVs*	Window**	AV1	Window**	AV3, 6, 9	Window**	Subsample
10	HRT Interview	H[1] (all)	-3 / +3	H[1] (all)	-3 / +3					
17	CaD Interview	C[2](all)	-3 / +3	C[2](all)	-3 / +3					
33	Medical History	X (all)	-3 / +3							
35	Personal Habits					X	-6 / +18	X	-6 / +30	
38	Daily Life					X	-6 / +30	%X	-6 / +30	6%
39	Cog Assessment					%H	-6 / +18	%H	-6 / +30	HRT > 65
44	Current Medications					X	-6 / +18	X	-6 / +30	
45	Current Supplements					X	-6 / +18	X	-6 / +30	
53	HRT Calendar[4]	H (SAV1)	-3 / +3			H	-3 / +18			
60	FFQ			%D (AV2+)	- -6 / +12	D	-6 / +12			33% AV2+
80	Physical Measures			X (all)	-6 / +6					
	Hip/Waist[3]					X	-6 / +18	%X	-6 / +30	6%[6]
81	Pelvic[4]			H (all)	-12 / +6					
82	EA[4]							%H	-12 / +24	5%
84	Clinical Breast Exam			H (all)	-6 / +6					
85	Mammogram			H (all) D (AV2, 4, 6, 8)	-12 / +6 -24 / +6					
86	ECG							X	-6 / +30	
87	BD					BD	-6 / +18	BD	-6 / +30	
90	Functional Status					%X	-6 / +18	%X	-6 / +30	25% > 65
92	Pap[5]							H	-12 / +24	
100	Blood					X	-6 / +30	%X	-6 / +30	6%
101	Urine					BD	-6 / +18	BD	-6 / +30	
950	Pill Dispensing	H (SAV1)	-3 / +3	H (AV2+) C (all)	-6 / +6 -6 / +6	H	-3 / +6			
951	Pill Adherence	H (SAV1)	-3 / +3	H (AV2+) C (all)	-6 / +6 -6 / +6	H	-3 / +6			

See next page for footnotes.

Table 16.1
Time Limits for Collecting Tasks
OS

Task	Name	AVs* excluding AV3	Window**	AV3	Window**	AV6	Window**	AV 9	Window**
33	Medical History	X (AV1) X (AV2) X (AV4+)	-2 / +10 -2 / +9 -2 / +10	X	-6 / + 15[7]				
38	Daily Life			X	-6 / +15				
44	Current Medications			X	-6 / +15				
45	Current Supplements			X	-6 / +15				
48 143 144 145 etc.	OS Follow-up Forms	X (AV1) X (AV4) X (AV5+)	-2 / +10 -2 / +10 -2 / +10	X	-6 / +15				
60	FFQ			X	-6 / +15				
80	Physical Measures			X	-6 / +15	BD (Ht/Wt)	-3 / +15		
87	Bone Density			BD	-6 / +15	BD	-3 / +15	BD	-3 / +15
100	Blood Collection			X	-6 / +15				
101	Urine			BD	-6 / +15			BD	-3 / +15

Key:

X = All participants
H = HRT
D = DM
C = CaD
BD = BD sites
% = Subsample of participants, description in Subsample column
* = applicable contacts given in parentheses ( ).
** = number of months before (-) and after (+) the contact target date.

1 = Active in HRT and 2 routine contacts after stopping (e.g., at next semi-annual and annual contacts)
2 = Active in CaD and 1 routine contact after stopping (e.g., at next semi-annual or annual contact)
3 = Hip/Waist not currently monitored on Task Completeness Report
4 = With Uterus
5 = With Cervix
6 = Same as the 6% blood draw subsample
7 = If Year 4 Form 33 from mailing has been completed, do not collect the Year 3 Form 33.

Time limits are the same as the expanded windows for *WHIP 1445 – Task Completeness.*

16.4.2.1 Hormone Replacement Therapy (Required)

The following minimum safety procedures must be completed and reviewed for safety concerns before an HRT participant is given HRT study pills. See *Table 16.2 – Follow-up Clinical Examinations/Minimum Safety Requirements for HRT Participants.* It is recommended that safety exams performed by outside providers be done within 6 months of the annual visit. Any abnormal reports should be thoroughly investigated and documented:

- Clinical breast exams are required annually for pills to be dispensed. The CBE may be done at a CC visit or by an outside provider. See *Section 9.7 – Clinical Breast Exam (Required)* and *Table 16.2 – Follow-up Clinical Examinations/Minimum Safety Requirements*.
- Mammograms are required annually. Participants may still receive a 6 month supply of HRT study pills at the annual visit, even if the annual mammogram has not been scheduled. However, the mammogram must be scheduled and a satisfactory report obtained by the semi-annual contact for an additional 6-month supply of HRT study pills to be dispensed. Do not dispense HRTstudy pills if more than 18 months have elapsed since the date of the last mammogram.
- Pelvic exams (for HRT participants with a uterus only) are required annually. See *Section 9.9 – Pelvic Exam and Pap Smear (Required)* and *Table 16.2 – Follow-up Clinical Examinations/Minimum Safety Requirements*.
- Pap smears are required in years 3, 6, and 9 although they can be offered to participants annually. See *Section 9.9 – Pelvic Exam and Pap Smear (Required)* and *Table 16.2 – Follow-up Clinical Examinations/Minimum Safety Requirements*.
- *Form 10 - HRT Management and Safety Interview* is required to be collected annually. This form may be completed at a CC visit or by phone. *Form 10A* may be mailed to participants for semi-annual visits only. (See *Section 5 - HRT* for more details.) A participant who can no longer communicate may continue on HRT study pills only if she has a proxy respondent approved by the CC Consulting Gynecologist and/or Principal Investigator (PI). An approved proxy should be a caregiver to the WHI participant (i.e., someone concerned about and involved with her health care). The required *Form 10* may be completed by an approved proxy at a CC visit or by phone (but not by mail). (See *Vol. 2 – Procedures, Section 16.6 – Follow-Up by Proxy.)*
- The *HRT Handbook* must be offered each time study pills are dispensed.
- A participant may continue on HRT study pills without the completion of *Form 33 - Medical History Update* with the expectation she may resume full participation in future years.

16.4.2.2 Calcium/Vitamin D (Required)

The following minimum safety procedures must be completed and reviewed for safety concerns before a CaD participant is given CaD study pills:

- *Form 17 - CaD Management and Safety Interview* annually. This form may be completed at a CC visit or by phone. *Form 17A* may be mailed to participants for semi-annual visits only. (See *Section 7 - CaD* for more details.) A woman who no longer can communicate may continue on CaD study pills only if she has a proxy respondent approved by a CC physician and/or PI. An approved proxy should be a caregiver to the WHI participant (i.e., someone concerned about and involved with her health care). The required forms may be completed by an approved proxy at a CC visit or by phone (but not by mail). (See *Vol. 2 – Procedures, Sec. 16.6 – Follow-up By Proxy*).
- The *CaD Handbook* must be offered each time study pills are dispensed. A participant may continue on CaD study pills without the completion of *Form 33 - Medical History Update* with the expectation that she may resume full participation in future years.

Table 16.2

Follow-up Clinical Examinations/Minimum Safety Requirements for HRT Participants

Exam/Procedure	Protocol-Defined Frequency	If Participant refuses procedure at CC, What is Acceptable?*	Minimum Safety Requirements (for participants to stay on study pills)*
Clinical Breast Exam (*Form 84*)	Annually	CBEs should be done in the CC. If the participant refuses to have the CBE done at the CC, a written or verbal report of an outside provider exam must be obtained from a clinician. A report of "normal" is acceptable.	Same
Pelvic Exams (women with uteri) (*Form 81*)	Annually	Pelvic exams should be done in the CC. If a participant refuses to have the exam done at the CC, a written or verbal report of an outside provider exam must be obtained. Verbal reports from participants will only be accepted in years 2, 4, 5, 7, or 8. A report of "normal" is acceptable.	If a participant refuses to have the exam done at the CC, a written or verbal report from a clinician for an outside provider exam must be obtained in years, 3, 6, and 9. A report of "normal" is acceptable.
Pap Smears (women with cervices) (*Form 92*)	Years 3, 6, and 9	They may be done annually with the pelvic exam. If a participant refuses to have a pap smear done at the CC, a written or verbal report of an outside provider exam must be obtained.	Same
HRT Safety Interview Management (*Form 10*)	Semi-annually and annually	*Form 10* may be completed at a CC visit or by phone. *Form 10A* may be mailed to participants at semi-annual visits only.	Annually
Mammograms (*Form 85*)	Annually	Mammograms from other institutions are acceptable.	18 months

*Note: If a participant refuses a recommended diagnostic follow-up exam/procedure for an abnormality, study pills may need to be discontinued. *Refer to section 5 – HRT* for specifics.

16.4.2.3 Dietary Modification

A DM intervention participant may continue to attend DM sessions without participating in any follow-up procedures, with the expectation that she may resume full participation in future years.

16.4.3 Guidelines for Restarting Participant who Discontinued Pills for 12 Months or More

16.4.3.1 Restarting HRT

See *Section 5.5.4.1 – Guidelines for Restarting a HRT Participant who Discontinued Pills for 12 Months or More*

Table 16.3 – Options for WHI Task Completion

Form#	Form Name	Current Options					Comments
		CC Visit[1]	Mail	Phone Priority[2]		Outside Provider	
				High	Low		
10	HRT Management and Safety Interview[3]	X	X	X			HRT while on study pills and 2 subsequent contacts (eg., semi-annual and annual) if off intervention
17	CaD Management and Safety Interview[4]	X	X	X			CaD while on study pills and 1 subsequent contact (eg. One semi or annual) if off intervention
100	Blood Collection	X					CT subsample, OS AV3
101	Urine Collection	X					Bone density sites
143-148	OS Exposure Update	X	X		X		
20	Personal Information Update	X	X	X			
33/33D	Medical History Update/Detail	X	X	X			
35	Personal Habits Update	X	X		X		CT only
38	Daily Life	X	X		X		CT subsample (blood subsample), OS AV3
39A/B	Cognitive Status	X					HRT ≥65 only
40	Addendum to *Form 33*	X	X		X		One-time only
44	Current Medications	X			X		
45	Current Supplements	X			X		
60	FFQ	X	X				DM subsample, OS AV3
80	Physical Measurements	X					CT (waist and hip in subsample only), OS AV3
81	Pelvic[3]	X				X	HRT only. Refer to an outside provider only if participant refuses to have it in-clinic (verbal report of a normal exam is not acceptable at AV3, AV6, or AV9).
82	Endometrial Aspiration	X				X	HRT subsample or according to bleeding management procedures in *Vol. 2, Section 5 – HRT*. Refer to an outside provider only if participant refuses to have it in-clinic.
83	Transvaginal Uterine Ultrasound	X				X	HRT only; ultrasounds are done at some CCs, but are not routine in-clinic procedures
84	Clinical Breast Exam[3]	X				X	HRT only (option in DM). Refer to an outside provider only if participant refuses to have it in-clinic.
85	Mammogram[3]	X				X	CT only, mammograms are done at some CCs, but are not routine in-clinic procedures
86	ECG	X					CT only
87	Bone Densitometry	X					Bone density sites only
90	Functional Status	X					Subsample of CT participants 65 or older
92	Pap[3]	X				X	HRT only
WHILMA	Study Pill Adherence	X	X	X			HRT/CaD only, collections can be done in-clinic or by mail (estimates can be done over the phone).

[1]In clinic or at an appropriately equipped remote site.

[2]High phone priority means that the task is a study priority, and you should attempt phone completion as an early option. Low phone priority means that phone completion should be attempted only after all other options to complete the task have been thoroughly exhausted.

[3]Required for staying on HRT study pills.

[4]Required for staying on CaD study pills.

16.5 OS Annual Mail Contact and Follow-Up of Non-Responders

Follow-up data are collected annually from OS participants during the nine years following enrollment. Activities to collect the data consist of a series of mail and telephone contacts during the follow-up period. Data collection attempts by mail (Contacts 1-4) are conducted by the Clinical Coordinating Center (CCC) on an annual basis, except for participant year 3 when the data are collected by the CC during the follow-up clinic visit. For participants who do not respond to Contacts 1-4, data collection attempts by telephone (Contacts 5-6) are conducted by the CCs on an every-other-year basis (participant years 1, 5, 7, and 9).

16.5.1 CCC Responsibilities for Annual OS Follow-Up

A series of mail contacts to collect follow-up data from OS participants is conducted annually by the CCC, except in year 3 when the CC conducts the Year 3 Visit. The CCC is responsible for all printing (through the Government Printing Office [GPO]), assembly, and outgoing postage costs for the mail contacts. The four mail contacts include:

- An initial mailing of the entire questionnaire packet (Contact 1).
- A reminder/thank-you postcard (Contact 2). (Discontinued as of May 1997).
- A second mailing of the entire questionnaire packet (Contact 3).
- A third mailing of the entire questionnaire packet (Contact 4).

Spanish-language versions of the contact materials are mailed to participants whose primary language is Spanish, as indicated either by the "Preferred Language" flag on the Contact Information Screen in WHILMA (see *Vol. 5 - Data Systems*) or by prior completion of a Spanish-language *Food Frequency Questionnaire (Form 60S).*

16.5.1.1 Mailing of Annual OS Questionnaire Follow-Up Packet 1 (Contact 1)

A follow-up packet is mailed annually by the CCC to all OS participants (except those whose participation status in WHILMA is set to no mail contact, no follow-up contact, deceased, lost to follow-up, or absolutely no follow-up) two months before the participant's enrollment anniversary month. The exception to this schedule is during participant Year 3, when a clinic visit is scheduled. The packet includes a cover letter with a CC telephone number listed (see *Figure 16.1 - Cover Letter for OS Contact 1 (Year 1)* ; a postage-paid, CC-addressed return envelope with business reply information; a *Form 33 - Medical History Update* with the date of the last WHI medical update; and an OS Follow-Up Questionnaire, as appropriate. For Year 1, the *OS Follow-Up Questionnaire* is *Form 48*; for Year 3, it was *Form 143*; for Year 4, it is *Form 144*; for Year 5, it is *Form 145*. There is no *Follow-Up Questionnaire* for Year 2.

The *Form 33* has two labels:

1) **Date Label**: a Date Label with date of the last WHI medical update (last *Form 33* or date of enrollment for Year 1), OS contact number and corresponding barcode, participant year, and participant ID.

2) **Participant ID label:** a Participant Identification Label with participant name, participant ID and barcode, OS contact number, and participant year.

The *OS Follow-Up Questionnaire* (e.g., *Form 48*) has one label, a Participant Identification Label, with participant name, participant ID and barcode, OS contact number, and participant year.

The packet is sent third-class (bulk) mail in a mailing envelope printed with the CC's return address, the CCC bulk mailing permit number, and a request for notification of change of address.

16.5.1.2 Mailing of the Thank You/Reminder Postcard (Contact 2 – Discontinued in May 1997)

During the first year of mailing, a postcard (see *Figure 16.2 - Follow-up Postcard for OS Contact 2*) was mailed by the CCC to all OS participants one month after the mailing of the Contact 1 packet. The postcard served to thank those participants who had completed and returned their forms, and to remind those who had not returned their forms to please do so. Because the postcard did not increase response rates, it was discontinued in May 1997.

16.5.1.3 Second Mailing of Entire Follow-Up Packet (Contact 3)

A second complete follow-up packet is mailed during the participant's enrollment anniversary month (three months after the mailing of Contact 1) to those participants who did not respond to the first mailing (i.e., those who did not complete and return the form sent in Contact 1 and for whom the CC has not indicated receipt in WHILMA). The packet includes: A cover letter (different from the Contact 1 cover letter - *see Figure 16.3 - Cover Letter for OS Contacts 3/4 (Year 1)*) with CC telephone number listed; a postage-paid, CC-addressed return envelope with business reply information printed on the envelope*; Form 33 - Medical History Update*; and *Form 48 - OS Follow-up Questionnaire* (for Year 1).

The packet is sent third-class (bulk) mail in a mailing envelope printed with the CC's return address, the CCC bulk mailing permit number, and a request for notification of change of address.

16.5.1.4 Third Mailing of Entire Follow-Up Packet (Contact 4)

A third packet (identical to the Contact 3 packet) is mailed three months after the enrollment anniversary month (two months after Contact 3) to non-responders only (i.e., those who have not completed and returned the forms sent during earlier contacts and for whom the CC has not indicated receipt in WHILMA).

16.5.2 CC Responsibilities During Annual OS Follow-Up Mailings (Required)

The CCs have several responsibilities during mail Contacts 1-4. These responsibilities consist primarily of:

- Updating WHILMA to reflect that *Form 33* has been completed and returned.
- Making address corrections as soon as they become available.
- Completed forms are returned directly to CCs in the business-reply envelopes provided in the packet. Clinical Centers are responsible for paying the postage for these completed, returned forms.

16.5.2.1 Processing Returned Packets (Contacts 1-4) (Required)

Clinical Center staff are responsible for indicating in WHILMA that packets have been returned to the CC. When a packet is received at the CC, it is important to note its return immediately to prevent additional mailings from being sent to participants.

Return of a packet can be indicated in one of two ways: by using the "OS Receipt Screen" in WHILMA or by data entering *Form 33* and/or the OS follow-up form for that year (e.g., *Form 48*). (See *Vol. 5 - Data System.*)

Option 1: Using the "OS Receipt Screen"

- Remove *Form 33* and/or the OS follow-up form (e.g., *Form 48*) from the envelope.
- Scan the Participant ID barcode on the Participant ID Label on the top of either form.
- Indicate the OS contact number. This can be done in one of two ways:

  a) Scan the OS contact ID barcode on the *Form 33* Date Label, and press **F10** to save the data, or

b) Enter the contact number, which is listed on both the Participant ID Label (on *Forms 33* and *48*) and the Form 33 Date Label (e.g., label reads C3, enter 3), and press **F10** to save the data.

Option 2: Data entry of *Form 33* and/or the OS follow-up form (e.g., *Form 48*).

Using the first option is preferable because receipt of the packet needs to be indicated immediately and the CCC needs to know the OS contact number to evaluate the effectiveness of the various contacts.

Regardless of which option is chosen to indicate the return of the packet, the forms still need to be data entered. Before data entry, complete the top part of the forms. "Date Received", "Contact Type", and "Type of Visit" can be completed by the person opening the packet of forms. For "Date Received", fill in the day the packet is received at the CC. For "Contact Type", indicate "Mail". For "Visit Type", indicate "Annual" and fill in the visit year number, which can be found in the lower right-hand corner of the Participant ID Label (e.g., label reads Y1, record 01 on the form). The form should then be passed on to the appropriate person(s) for review, who should then complete the "Reviewed by" field on the form. Participants who have left entire pages blank on any of the return forms or who have not completed questions 4 through 7 on *Form 33* (these items are necessary to trigger a *Form 33D - Medical History Update (Detail*)), should be telephoned to collect the missing data. Refer to *Volume 8, Section 2 - Ascertainment and Form 33D* Forms Instruction for procedures for participants requiring completion of a *Form 33D - Medical History Update (Details).*

Incomplete Packets:

If a packet containing only one form is returned, the CC should still indicate that the packet has been returned using the procedures described above (to stop further mailings to that participant). Participants with missing forms will appear on *WHIP 1207 - Returned Packet with Missing Form*, which should be run monthly. Missing forms are those that have *not yet been data entered*. *WHIP 1207* includes the participant name and ID, date packet was received, and a message indicating which form is missing.

Clinical Centers are responsible for following up to collect data on missing forms. To follow-up on missing forms:

1) Check within the CC to make sure that the form is indeed missing. It may have been returned, but not yet data entered.

2) If the form is missing, CCs may use whatever methods they choose to collect the data on the missing form (e.g., they may use telephone, mail, both, etc.).

Names continue to appear on *WHIP 1207* until the missing form has been data entered or until Contact 5 (CC data collection by telephone) is initiated. At that point, if the missing form is *Form 33*, it will appear on *WHIP 1206 - OS Enrolled Members Needing Clinic Follow-Up*. The result of data collection attempts do not appear on *WHIP 1207* once the Contact 5 period has been reached (e.g., if a *Form 33* is completed after Contact 5 starts [but the *OS Follow-Up Questionnaire* is not completed] the follow-up questionnaire will not appear on *WHIP 1207*).

16.5.2.2 Making Address Corrections (Required)

Clinical Center staff are responsible for updating WHILMA to reflect any participant address changes. Each packet mailed out to OS participants has their CC's return address in the upper left-hand corner, with the line "Address Correction Requested" underneath. In the event that the participant's address on the mailing envelope is incorrect, the U.S. Post Office (USPO) will notify someone at the return address printed on the envelope. The USPO will not actually return the envelope, but will provide a photocopy of the envelope and a statement as to why it was not delivered. If the address has been changed, the new address will be provided. If the address has changed and no forwarding address is available, it will be marked "undeliverable". The USPO will charge the CC for each packet that is not delivered ($.50 as of spring, 1996).

For **changed addresses where the new address is provided by the USPO**, update the address in the "Contact Information Screen" in WHILMA immediately. This will prevent future mailings from being sent to the undeliverable address (which would again cost the CC approximately $.50). It is a good idea to try reaching these participants by telephone to determine whether or not the telephone number has also changed. If it has, this information should also be updated in WHILMA.

When a participant has an **undeliverable address and a new address is not available**, set the "undeliverable address" flag on the "Contact Information Screen" immediately (see *Vol. 5 - Data System*). This will prevent future mailings from being sent to the undeliverable address. Initiate a search to find the correct address by contacting the participant and/or by using the information listed on *Form 20 - Personal Information*. Refer to *Section 17.3 - Locating "Hard to Find" Participants* for specific instructions for conducting a search for lost participants. Try to fix the address as soon as possible, so as not to lose permanent contact with the participant. Participants with an undeliverable address will appear on the *WHIP 1211 - Undeliverable Address Report* the next time it is produced (see *Section 16.5.2.3 - Running Monthly OS Follow-up Reports from WHILMA (Required)*).

When the USPO indicates that a participant is "deceased", initiate contact with persons listed *on Form 20 - Personal Information*. If a death is confirmed, complete *Form 7 - Participation Status and Form 120 - Initial Notification of Death* and process according to procedures outlined in *Volume 8 - Outcomes*.

Clinical Centers pay for the cost of USPO updates on address changes and non-deliverables ($.50 per update as of spring, 1996) and for the cost of completed forms mailed from participants to the CC.

16.5.2.3 Running Monthly OS Follow-up Reports from WHILMA (Required)

Several reports are available to help CCs keep track of the status of OS participant follow-up. Detailed instructions for running these reports in WHILMA are given in *Vol. 5 - Data System, Section 9.2 - Reports and Appendix D - WHILMA Reports*.

Every month, each CC should run the following reports:

1. *WHIP 0611 - Members With an Incomplete Address or Long Name/Address*. This report provides a list of participants with problem addresses (e.g., the address is incomplete or will not fit on a mailing label). Participants with address lines that are too long should be fixed immediately. An address line is too long if it appears on this report as more than one line. To fix the problem, use Address Line 2 for the second line of the address, or abbreviate words in the first line so that they stay within the 30-character width limit of the mailing labels.

   Addresses that are incomplete should be followed up on as soon as possible. If the zip code is missing, try calling the USPO, or if that fails, call the participant to obtain the complete/correct address. If you cannot fix the address right away, set the undeliverable address flag on the "Contact Information Screen" in WHILMA. This will prevent mailings from being sent to an undeliverable address. Incomplete addresses should be fixed within two weeks of appearing on *WHIP 0611*. Participants will continue to appear on this report until either the address has been fixed or the "undeliverable address" flag has been set. Once you have made all of the necessary edits indicated on the report, run the report again to confirm that problems have been cleared.

2. *WHIP 1211 - Undeliverable Address Report*. This provides a list of all (CT and OS) participants with undeliverable addresses in the CC's database. It does not include those with follow-up status 5-7 (no follow-up, deceased, lost to follow-up). Included on the report are the participant's name and (undeliverable) address; member ID; home phone; work phone; note indicating that the workplace should not be contacted, if applicable; best time to call; telephone numbers for other contact; follow-up status; and date marked (i.e., the date the undeliverable address flag was set).

   Undeliverable addresses should be updated as soon as possible, since a participant will not receive any mailings (such as OS follow-up data collection packets) until the address is fixed. If the participant does

not receive her mailings, the data will eventually need to be collected by CC staff (see *Section 16.5.3 - CC Data Collection for Non-Respondents to OS Mailings*). Also, the sooner you try to get an address correction, the more likely it is that you will be able to locate the participant. Undeliverable addresses should be corrected within one month of appearing on *WHIP 1211*. Participants will continue to appear on this report until the "undeliverable address" flag has been removed or follow-up status changes.

3. *WHIP 1207 - Returned Packet with Missing Forms*. This report lists participants for whom packets have been returned, but either one or both of the forms have not yet been data entered in WHILMA. Use this report to serve as a reminder to data enter the forms that have been returned or to follow-up with participants to collect data on forms that were not returned in the packet.

4. *WHIP 1206 - OS Enrolled Members Needing CC Follow-Up*. The purpose of this report is to provide a list of those participants who do not have a completed *Form 33* following the four CCC mailings (by two months after the mailing of Contact 4). A participant appears on this form if no *Form 33* has been data entered since Contact 1 was initiated and if her follow-up status is not any of the following: no follow-up, deceased, or lost-to-follow-up.

   This report lists participant name, participant ID, home phone number, work number, best time to call, phone of other contact, and follow-up status. As described below in *Section 16.5.3 - CC Data Collection for Non-Respondents to OS Mailings*, CCs should use this report as a prompt to initiate follow-up contacts to participants who have not completed a *Form 33*.

   Participants remain on this report until one of the following occurs: either a *Form 33* has been completed; follow-up status changes; or the next year's contacts begin.

   In addition, the *WHIP 1210 - OS Follow-up Receipt Report*, can be run on an as-needed basis. This report lists packets that have been received and processed (as described in *Section 16.5.2.1 - Processing Returned Packets (Contacts 1-4)* at the CC. The report lists participant name and ID, receipt date, contact number, and employee ID.

16.5.3 CC Data Collection for Non-Respondents to OS Mailings (Required)

During participant years 1, 5, 7, and 9, CCs are responsible for collecting *Form 33 - Medical History Update* data on those participants who have not responded to that year's mailings. (*Form 33* data are also collected by CCs during the participant's Year 3 follow-up visit.) If a participant has not responded to Contacts 1-4 during applicable years, CC staff should initiate telephone contacts to collect the data. This is done through a series of attempts to reach the participant or her proxy to collect the data. Non-respondents needing follow-up data collection are listed on *WHIP 1206 - Members Needing CC Follow-Up* (a report generated monthly by the CC).

Clinical Center OS follow-up data collection activities consist of two types of contacts: a phone contact to ascertain correct address and to collect *Form 33- Medical History Update* from the participant (Contact 5), and, if applicable, a mail or phone contact to trace participants and/or collect *Form 33* data from a proxy (Contact 6).

16.5.3.1 Telephone Contact to Ascertain Correct Address and to Collect Medical History Update (Contact 5) (Required)

If *Form 33* has not been returned by two months after the third mailing of the OS follow-up packet (CCC Contact 4) during participant years 1, 5, 7, and 9, the CC should attempt to reach the participant by telephone. The purpose of this call is to confirm that the correct address is shown in WHILMA and to complete *Form 33 - Medical History Update*. Use the Members Needing CC Follow-Up report to determine which participants require follow-up telephone contacts.

Actual contact is required with the participant at this point to confirm that we have the correct address and phone number for her (e.g., a message left on an answering machine reminding her to mail in the packet is not sufficient since there is no way to confirm that she has even received the packet or the phone call).

When calling, make at least 8 telephone attempts the first month and 4 attempts the second month during the "best times to call" (identified on *Form 20 - Personal Information*). Refer to *Figure 16.4 - Suggested Script for OS Contact 5 Telephone* Contact. If contact is made with the participant, verify the address and complete Form 33 over the telephone. *WHIP 0441 - Personal Information Update*, an update *of Form 20 - Personal Information* can also be completed at this time. Completion of the *OS Follow-Up Questionnaire* (if applicable for that year) is optional, depending on the success in reaching completion goals for that form.

If you determine that the telephone number and/or address have changed, update WHILMA accordingly. If a participant requests a change in her participation status, initiate a *Form 24 - Retention Worksheet* (see *Section 17.2 - Clinical Center Activities for Retention Challenges*). If you find out that she is deceased, complete *Form 7 - Participation Status* and *Form 120 - Initial Notification of Death* and process according to *Volume 8 - Outcomes*.

Clinical Centers have the option of mailing a *Form 33* (and *OS Follow-Up Questionnaire*, if applicable) to participants who, as determined by the phone contact, are willing to complete the form but are unwilling to complete it over the phone.

If telephone attempts fail to make contact with the participant, contact a proxy to determine the location and vital status of the participant (Contact 6). After proxy contact, continue to try to locate and interview the participant, if appropriate. Do not interview the proxy unless the participant is deceased, unable to communicate, or has poor cognitive functioning. (See *Section 16.6 - Follow Up by Proxy*.)

16.5.3.2 Mail/Phone Contact to Trace Participant and/or Collect Medical History Update from Proxy (Contact 6) (Required)

If telephone attempts to make contact with the participant fail, contact a proxy to determine her location and vital status. Use *Form 20 - Personal Information* for information on where to locate proxy contacts. When contacting proxies, use the following order of priority: 1) spouse or partner; 2) nearest relative; 3) friend; 4) physician. Refer to *Figure 16.5 - Suggested Script for Proxy Telephone Contact*.

If the proxy indicates that the participant is able to be interviewed, ascertain the new address and telephone number and continue trying to locate and interview her. If the participant has a new address, update the database with the address correction.

If the participant is deceased, unable to communicate, or has poor cognitive functioning, collect *Form 33* data from a proxy by either telephone or mail. For mail contacts, refer to *Figure 16.6 - Sample Cover Letter for Proxy Contact*. The *OS Follow-up Questionnaire* (e.g., *Form 48, 144, 145*) is not collected by proxy.

The CC is responsible for keeping track of which of their participants require Contact 6.

16.6 Follow-Up by Proxy (Required)

Some follow-up contacts, because of a participant's illness, disability, or death, may need to be conducted by proxy. A proxy "stands in" for the participant and provides information about her health. The proxy should be someone who has frequent contact with the participant and knowledge of her health status.

16.6.1 Designating a Proxy (Required)

Clinical Centers must have IRB approval to correct participant data from a proxy if the participant's consent form does not include explicit approval for contact of personal contacts.

Approval to conduct follow-up contact(s) by proxy should be a careful decision based on the participant's situation and the individual proposed to serve as her proxy. Obtain approval to conduct contacts by proxy from the participant or her legal next-of-kin, if possible. Proxy contacts must be also approved by the CC PI and other CC investigators, consultants, and/or staff, as determined at your CC.

Once a proxy has been identified, establish contact with that person(s) and discuss how that person was identified as the proxy (e.g., listed as a close contact or her personal physician). Determine if s/he has any questions about the study and/or the proxy role. Provide the proxy with relevant information about the study (e.g., consent, information sheets). Ongoing efforts to promote rapport and retention with the participant should also extend to your contacts with the proxy.

Complete a new *WHIP 0441 - Personal Information Update* and *Form 7 - Participation Status*, as appropriate, to reflect the proxy contact information and appropriate follow-up status.

16.6.1.1 For CT Participants Attending Clinic Visits

Clinic staff collect proxy names and contact information from CT participants attending their annual or semi-annual clinic visits. To collect the information, the participant is provided with a copy of the *Proxy Update (Vol. 2, Appendix F, Figure F.3.13)* to review and discuss with staff. This update explains the purpose and role of the proxy. After the woman reviews the update and has had an opportunity to discuss the role of the proxy with clinic staff, she is asked to designate her proxy and provide the proxy's contact information (address and phone number). At the same visit, the participant is given two copies of the *Proxy Update*: one for her and one for her proxy. In addition, she fills in her proxy's name and signs her own name on the *Proxy Letter (Vol. 2, Appendix F, Figure F.3.14)*. The *Proxy Letter* informs the proxy that he/she has been selected by the participant to serve as her proxy. Instruct the participant to either give or mail a copy of the *Proxy Update* and *Proxy Letter* to her selected proxy. Be sure to provide a postage-paid envelope addressed to the proxy if he or she does not live with the participant.

Data enter the proxy contact information in the Personal Information screen in WHILMA. At each subsequent clinic visit have the participant review and update, as appropriate, the proxy contact information as part of her routine Personal Information review.

Participants have the option of refusing to name a proxy or provide contact information.

The *Proxy Letter* instructs the proxy to contact the CC if he/she has questions. It is the CC's responsibility to include their contact information on the letter, either by using a stamp, affixing a label or business card, hand-writing the information, or running the letter through a laser printer.

Local IRB approval of the materials and procedures is required before collection of proxy contact information can begin. If the local IRB requires changes to the materials or procedures, CCs may modify them as requested. Revised materials should be submitted to the CCC for review before use.

The *Proxy Update* and *Proxy Letter* are ordered from the CCC using *Form 172 – Supplies Order*.

16.6.1.2 For OS Participants Attending AV3

Starting in summer 2000, clinic staff should collect proxy contact information from OS participants attending their AV3. To collect the information, use the same procedures described in *Section 16.1.1.1 – For CT Participants Attending Clinic Visits.*

16.6.1.3 For OS Participants Beyond AV3

At the time the procedures to designate a proxy were developed, most OS participants had already attended their AV3. Proxy contact information for these participants is collected through a one-time, first class mailing initiated by the CCC in early 2001. The mailing consists of a cover letter explaining the purpose of the mailing, a copy of the *Proxy Update*, a copy of the *Proxy Letter*, a copy of the Personal Information Sheet imprinted with the participant's information, and a Business Reply Mail envelope imprinted with the CC's address. Participants are asked to make relevant updates to the Personal Information Sheet, as well as to provide proxy contact information, and to send the sheet back to the CC. The proxy contact information and any changes to the personal information are data entered in WHILMA at the CC.

16.6.1.4 For Participants Who Do Not Have a Designated Proxy

If a participant has not designated a proxy, or if the proxy is deceased, cannot be located, refuses contact, or is unable to participate, CCs may (subject to local IRB approval) contact one of the participant's other personal contacts to serve as the proxy.

When using other personal contacts to collect proxy information, in order of data collection preference, contact:

- Spouse or partner
- Other close family member
- Close friend
- Health care provider

16.6.2 Proxy Follow-Up Contact Procedures (Required)

Clinical Centers must have IRB approval to collect participant data from a proxy if the participant's consent form does not include explicit approval for contact of proxies or personal contacts.

Follow-up contacts with a proxy for CT participants should preferably take place by phone or visit, rather than by mail (see *Figure 16.5 - Suggested Script For Proxy Telephone Contact*). Follow-up contacts with a proxy for OS participants can take place by mail (see *Figure 16.6 - Sample Cover Letter for Proxy Contact*), if necessary. When the proxy is first contacted by the CC, discuss how that person was identified as the proxy (e.g., designated by the participant, listed as a personal contact). Determine if s/he has any questions about the study and/or the proxy role. Provide the proxy with relevant information about the study (e.g., Proxy Update, consent forms, study information sheets), as needed. Any ongoing efforts used to promote rapport and retention with the participant should also extend to your contacts with the proxy.

If the participant is alive, each proxy contact should be preceded by a discussion of the participant's ability to resume her own follow-up contacts, depending on her particular situation. If it has not been done, complete a *Form 7 - Participation Status*, to reflect that she is on "Proxy follow-up" and to indicate any changes to her intervention status, as appropriate (see *Vol. 2, Section 16.4.2 – Minimum Procedures Required for a CT Participant to Remain on Intervention* for details on keeping "proxy follow-up" participants on intervention).

If the participant is deceased, details on proxy follow-up outcomes information are described in *Vol. 8 - Outcomes, Section 7 – Fatal Events.*

16.6.2.1 Proxy Follow-Up Procedures for CT Participants (Required)

For CT women who are alive, conduct twice yearly contacts with the designated proxy. The only data to be completed by proxy (if scheduled) are:

- *Form 10 - HRT Management and Safety Interview (HRT).*
- *Form 17 - CaD Management and Safety Interview (CaD).*
- *Form 33 - Medical History Update* and, if appropriate, *Form 33D - Medical History Update (Detail).*
- *WHIP 0441 - Personal Information Update.*
- *Form 950 - Medication Adherence.*

For CT women who are deceased (see *Vol. 8 - Outcomes, Section 7 – Fatal Events*), collect:

- *Form 120 – Initial Notification of Death*
- *Form 33 - Medical History Update* and, if appropriate, *Form 33D - Medical History Update (Detail).*

16.6.2.2 Proxy Follow-Up Procedures for OS Participants (Required)

The CCC does not mail annual follow-up packets to OS participants (or their proxies) if the follow-up status is listed as "proxy" on *Form 7 – Participation Status*. It is the CC's responsibility to contact the proxy and collect the data, preferably by phone. OS participants who are on "proxy follow-up" automatically appear on *WHIP 1206 – OS Members Needing CC Follow-up*, along with the participant's contact information, follow-up status, and date of last *Form 33 – Medical History Update*. To get the proxy contact information, see the participant's Personal Update Screen. CCs should run this report every month to see which of their OS participants require CC follow-up. This report can be run to show participants needing follow-up for all years (i.e., AV1, AV2, AV4, AV5, etc.), for a select year (e.g., AV5 only), or for odd-numbered years only (e.g., AV1 and AV5).

For OS women on proxy follow-up who are alive, collect *Form 33 - Medical History Update, Form 33D – Medical History Update (Detail)*, if appropriate, and *WHIP 0441 - Personal Information Update* with the proxy during years 1, 3, 5, 7, and 9 post-randomization. For OS women on proxy follow-up who are deceased, collect *Form 120 – Initial Notification of Death* and *Form 33 – Medical History Update* and, if appropriate, *Form 33D – Medical History Update (Detail).*

For additional information about proxy follow-up of OS participants, *see Section 16.3 – CC Data Collection for Non-Respondents to OS Mailings.*

16.6.3 Using Proxies to Obtain Medical Records

The role of the proxy in obtaining medical records is determined by local state and institutional laws and policies. The designated proxy, especially if she/he is a family member or has medical power of attorney, may be able to sign medical releases. CCs will need to contact their local IRB and medical institutions for information and policies on this issue.

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16.7 Follow-up of Participants with Less than Full Participation Status (Required)

For women with less than full participation status, the general principle is to continue the WHI tasks (see in *Vol. 1 - Study Protocol and Policies, Table 1-A1.2 - Frequency of Collection*) for the woman's component (HRT, DM, CaD, OS) to the extent possible given her participation status. Specific situations are given below, as examples.

16.7.1 Participants Who Have Stopped Intervention (CT) (Required)

"Stop HRT", "Stop DM," or "Stop CaD" status: For a CT participant who has stopped her intervention(s), continue with the twice yearly CC visit tasks (see *Vol. 1 - Study Protocol and Policies, Table 1-A1.2 - Frequency of Collection*, and *Sections 16.2 - Semi-Annual Contact (CT only) (Required) and 16.3 - Annual (CT) and Third-Year (OS) Visit (Required)*). Specifically, continue with all forms and procedures on the visit plan, including safety procedures and forms (excluding *Form 950 - Medication Adherence*), if the participant is willing. If there are no issues that contraindicate resuming the intervention, inquire about the participant's willingness to start the intervention again (see *Section 17.4.5 - Reactivation of Participants with Changes in Participation Status*).

Additional considerations for participants who have stopped HRT or CaD include:

- Collect study pill bottles and enter adherence information into WHILMA when the participant stops her study pills.
- Complete *Form 10 - HRT Management and Safety Interview* at the next **two** routinely scheduled visits or contacts after stopping HRT intervention.
- Complete *Form 17 – CaD Management and Safety Interview* at the next routinely scheduled visit or contact after stopping CaD intervention.

16.7.2 Participants On Partial Follow-up

The suggested procedures for partial or customized follow-up data collection are:

- When forms are mailed, include a cover letter, pencil, and return stamped envelope.
- Follow-up with a reminder phone call.
- Complete forms by telephone.

Certain minimum procedures are required for the HRT and/or CaD participant to continue on intervention even if she elects partial follow-up (refer to *Section 16.4.2 - Minimum Procedures Required for a CT Participant to Remain on Intervention*). If appropriate, as part of a phone call or cover letter, inquire if the participant is interested in resuming intervention (see *Section 17.4.5 - Reactivation of Participants with Changes in Participation Status*) or resuming CC visits.

16.7.2.1 CT Participants (Required)

For a CT participant who refuses further CC visits but will allow phone and/or mail contact, continue with twice-yearly completion of all forms that are scheduled in *Vol. 1 - Study Protocol and Policies, Table 1-A1.2 - Frequency of Collection* that can be completed by phone or mail.

The forms to be completed by phone or mail (if scheduled) are:

- *Form 10 - HRT Management and Safety Interview (HRT)*: phone only.
- *Form 17 - CaD Management and Safety Interview (CaD):* phone only.
- *WHIP 0441 - Personal Information Update*: phone or mail.

- *Form 33 - Medical History Update*: phone or mail.
- *Form 60 - FFQ (DM):* mail only.
- *Form 950 - Medication Adherence*: phone estimate of study pill count and then have the participant mail study pills in.

16.7.2.2 OS Participants (Required)

Observational Study women who refuse the Year 3 CC visit should complete *Form 33 - Medical History Update* and *WHIP 0441 - Personal Information Update* by phone.

Annual follow-up mailings will not be sent to OS participants who have requested "partial follow-up with no mail". For a woman in the OS who refuses mail contact but allows phone contact, complete the phone follow-up at years 1, 3 (unless she attends the CC visit), 5, 7, and 9 post-randomization. See *Section 16.5 - OS Annual Mail Contact and Follow-Up of Non-Responders* for suggested procedures.

16.7.3 Participants Who Are Lost-to-Follow-Up

Continue to search periodically for participants who are lost to follow-up. For procedures, see *Section 17.3 - Locating "Hard to Find" Participants*. Observational Study mailings are not sent to women who are "lost-to-follow-up" or who have an undeliverable address.

16.7.4 Participants on No Follow-Up

A letter or postcard (see model in *Figure 16.7 - Postcard for Participants on No Follow-Up*) should be sent or phone call made yearly to inquire if the participant would be willing to "rejoin" the WHI or if she would, at a minimum, complete *Form 33 - Medical History Update*. See *Section 17.4.5 - Reactivation of Participants with Changes in Participation Status*.

16.7.5 Participants on Absolutely No Follow-Up (Required)

No mail or phone contacts or attempts to collect data should be made with participants who have requested absolutely no follow-up.

16.8 Non-Routine Contacts

Non-routine contacts may occur for any WHI participants. These contacts give the CC the opportunity to continue efforts to build rapport and promote retention. Reasons why a participant may contact the CC non-routinely in person or by phone are detailed below along with brief information and references on how to manage such contacts:

- **Questions about the WHI study (perhaps in response to a recent news item):** The nature of the participant questions will determine the approach you take. Refer the participant to a CC staff person or investigator who has understanding of the issues involved with the news item or specific skill in responding to concerned participants (see *Section 17 - Retention*).

- **Questions or concerns about symptoms:** Symptom questions, in most instances, should be referred to the CP. Refer to *Section 5 - HRT and Section 7 - CaD* for detailed information on management of symptoms associated with the HRT and/or CaD interventions. Make reference to the *HRT Handbook* and/or *CaD Handbook*, as appropriate, or offer to send the participant another copy.

- **Questions about diagnostic reports (e.g., endometrial aspiration, mammogram):** Questions about specific findings should be referred to the CP. If the participant is requesting copies of the reports for herself or her health care provider, follow your CC's procedures for making such copies available.

- **Schedule or reschedule CC visits:** Schedule or reschedule routine CC visits as close as possible to the target window for that visit. Discuss with the participant the importance of keeping her visit appointments and thank her for her efforts to reschedule. Refer the participant to the appropriate CC staff person to initiate activities for retention challenges if she has rescheduled visits several times in the past (or has rescheduled the current visit several times) (see *Section 17.2 - Clinical Center Activities for Retention Challenges)*.

- **Report an outcome or other major event:** If the participant reports an outcome at a **non-routine** contact, remind her to record this information on her next routine medical history update. Interim reports of outcomes will not be processed. Follow local procedures for informing the CP of outcomes that may necessitate stopping study pills or reporting serious adverse experiences (see *Vol. 2 – Procedures, Section 5 – HRT* and *Section 7 – CaD*). CCs may also want to develop procedures for informing appropriate staff (e.g., the participant's Group Nutritionist) so that participant rapport and retention can be supported.

- **Provide new address or phone information:** Update the most recent *WHIP 0441 - Personal Information Update* report in the participant's file and provide this information to the appropriate data entry staff person to update the information in WHILMA.

Each of these non-routine contacts should be documented in contact notes contained in the participant's file along with any referrals or actions taken.

Figure 16.1

Cover Letter for OS Contact 1 (Year 1)

[PRINTED ON WOMEN'S HEALTH INITIATIVE LOGO LETTERHEAD]

Thank you for being part of the Observational Study of the Women's Health Initiative! The purpose of the Observational Study is to learn more about women's health and about the causes of disease in women. As a participant in the Observational Study you are asked to fill out forms each year so that we can update information on your health. This information will be used to learn more about the relation between lifestyle habits and health, and may also be used in related research by other scientists interested in women's health. We want the results of this study to represent **all** women, so your continued participation is very important to us.

Please complete the enclosed two forms. *Form 33 - Medical History Update* asks about your recent medical history and *Form 48 - Observational Study Follow-up* asks about your health habits and medication use. When you have completed the forms, please return them right away in the postage-paid envelope.

If you have any questions about the forms or need any help in filling them out, please call your Clinical Center at the telephone number listed on the attached page. For the next several years, we will need to know where to send your newsletter and health forms, so please call us if you move to a different address.

All information you provide will be kept confidential and your name will not be linked with data given to anyone other than the researchers in this study. Participation in this study is voluntary and you may refuse to answer any questions on the forms. However, it is very important that we have complete follow-up information on all participants to make sure that the results of the WHI are accurate and scientific.

We appreciate your continued participation in the Women's Health Initiative. This is an important study that may help us to improve the health of women for generations to come. Every woman counts, so please keep in touch.

Figure 16.2

Follow-up Postcard for OS Contact 2

[Discontinued in May 1997]

A few weeks ago a packet of forms was mailed to you from the Women's Health Initiative. If you have already completed and returned them, thank you very much.

If you haven't returned the forms, could you return them right away? It is very important that we have complete information on all participants so that the results of the Women's Health Initiative will represent the health of **all** women.

If your address on this postcard is not right, please call your Women's Health Initiative Clinical Center. If we don't receive your completed forms in the next several weeks, we will mail you another set.

Thank you for your continued participation in the Women's Health Initiative.

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Figure 16 .3
Cover Letter for OS Contacts 3/4 (Year 1)

[PRINTED ON WOMEN'S HEALTH INITIATIVE LOGO LETTERHEAD]

A few months ago we sent you a packet health forms to complete as a participant in the Observational Study of the Women's Health Initiative. We have not yet received your completed forms. In case the forms were misplaced or not received, new forms and a postage-paid envelope are enclosed.

The purpose of the Observational Study is to learn more about women's health and the causes of disease in women. As a participant in the Observational Study, you are asked to fill out a few forms each year so that we can update information on your health. This information will be used to learn more about the relation between lifestyle habits and health, and may also be used in related research by other scientists interested in women's health. We are writing to you again because we want the results of this study to represent **all** women, so your continued participation is very important to us.

Please complete the enclosed two forms. *Form 33 - Medical History Update* asks about your recent medical history and *Form 48 - Observational Study Follow-up* asks about your health habits and medication use. When you have completed the form, please return it right away in the postage-paid envelope.

If you have any questions about the forms or need any help in filling them out, please call your Clinical Center at the telephone number listed on the attached page. For the next several years, we will need to know where to send your newsletter and health forms, so please call us if you move to a different address.

All information you provide will be kept confidential and your name will not be linked with data given to anyone other than the researchers in this study. Participation in this study is voluntary and you may refuse to answer any questions on the forms. However, it is very important that we have complete follow-up information on all participants to make sure that the results of the WHI are accurate and scientific.

We appreciate your continued participation in the Women's Health Initiative. This is an important study that may help us to improve the health of women for generations to come. Every woman counts, so please keep in touch.

You are very important to the WHI, but we haven't heard from you yet. Please respond.

Figure 16.4
Suggested Script for OS Contact 5 Telephone Contact

The caller should telephone until she/he is able to reach the woman. Actual contact is required to confirm that the CC has the right address and phone number.

"Hello Mrs./Miss/Ms._____, this is _____ from the Women's Health Initiative **(name of clinical center)** ."

"Several weeks ago a form packet was mailed to you from the Women's Health Initiative. Did you receive the packet?"

If not received:

"I'm sorry to hear that. Maybe it was sent to the wrong address. Let me check your mailing address so that we can update our files."

(Record correct address, then continue.)

"Because your participation is very important to us and we would like to include your responses in the study results, I would like to go over one of the forms with you over the telephone. Is this a good time for us to complete the form over the phone?"

If no:

"When would you like me to call back?"

(Confirm time, thank participant, terminate call, call back later to conduct interview.)

If yes:

"Great. I will read you the questions over the telephone and record your answers."

Conduct interview: complete Form 33.

"Thank you very much for spending the time to answer these questions over the telephone. We're very glad to have you as part of the Women's Health Initiative.

(Terminate call.)

If yes:

"Good. Because your participation is very important to us and we would like to include your responses in the study results, I would like to go over one of the forms with you over the telephone. Is this a good time for us to complete the form over the phone?"

Figure 16.4 (continued)

If no:

"When would you like me to call back?"

(Confirm time, thank participant, terminate call, call back later to conduct interview.)

If yes:

"Great. I'll read you the questions over the telephone and record your answers."

Conduct interview: complete Form 33.

"Thank you very much for spending the time to answer these questions over the telephone. We're very glad to have you as part of the Women's Health Initiative.

(Terminate call.)

If during a contact it is determined that the participant is deceased, is unable to communicate, or has poor cognitive functioning, end call appropriately (e.g., if she is deceased *"I am so sorry to hear that Mrs./Miss/Ms._____ has passed away. She was an important member of our study."****):***

Go to Contact 6 - Mail/phone contact to collect data from proxy.

If at any point during the contact her participation status changes (e.g., she requests no further telephone contact):

Update Form 7 - Participation Status.

Initiate Form 24 - Retention Worksheet.

Figure 16.5
Suggested Script for Proxy Telephone Contact

Ask to speak to (in order of priority for contact):

spouse or partner

nearest relative

friend

Once contact is established, start at beginning of script.

If none of the above are available, contact the woman's physician.

"Hello, this is _____ from the Women's Health Initiative **(name of clinical center)** . May I speak to ***[proxy name]*****?"**

If proxy is available, continue.

If proxy is not currently available:

"Can you suggest a time when I may be able to call back and speak with him [her]?"

Confirm time, thank person on phone, call back later to talk with proxy.

If identified proxy continues to be unavailable after several calls, try to contact another proxy.

If participant is deceased:

"We were very sorry to hear that Mrs./Miss/Ms._____ has passed away. As you may be aware, she was an important member of our study, the Women's Health Initiative."

(Continue below.)

If participant is unable to communicate or has poor cognitive functioning:

"We were very sorry to hear that Mrs./Miss/Ms._____ has had a recent decline in her health. As you may be aware, she is an important member of our study, the Women's Health Initiative."

(Continue.)

"Because we want the study to represent **all** women, we would still like to include her in the results. In order to do this, I would like to ask you some questions about her health during the past year. Would this be a good time for me to ask the questions?"

Figure 16.5 (continued)

If yes:

Complete Form 33 - Medical History Update.

"Thank you very much for your help in the Women's Health Initiative. The information you have provided is very important to the results of the study."

If no:

"When would you like me to call back?"

(Confirm time, call back later to conduct interview.)

If husband/partner refuses to participate, thank him/her, terminate the call, and try to contact another proxy.

In order of priority for contact:

spouse or partner

nearest relative

friend

Once contact is established with new proxy, start at beginning of script.

If none of the above are available, contact the woman's physician.

For all participants, Update Form 7 - Participation Status, if it has not already been updated (e.g., regarding the participant's death or poor cognitive functioning).

Figure 16.6
Sample Cover Letter for Proxy Contact

[PRINTED ON WOMEN'S HEALTH INITIATIVE LOGO LETTERHEAD]

(If participant is deceased:)

We were very sorry to learn of your recent loss. As you may be aware, *[participant name]* was a valued participant in the Women's Health Initiative. The purpose of this study is to learn more about women's health and about the causes of disease in women. Therefore, it is important to us to learn about *[participant name]* 's health conditions. The information collected is used to learn about the relation between lifestyle habits and health, and may also be used in related research by other scientists interested in women's health.

(If participant is unable to communicate or has poor cognitive functioning:)

We are very sorry to learn of the decline in the health of your *[wife, sister, etc.], participant name]*. As you may be aware, *[participant name]* is a valued participant in the Women's Health Initiative. The purpose of this study is to learn more about women's health and about the causes of disease in women. All participants in the study are asked to fill out a few forms about their health each year during the length of the study. The information collected is used to learn more about the relation between lifestyle habits and health, and may also be used in related research by other scientists interested in women's health.

Because we would like to keep our information current, we are writing to ask that you complete a form about *[participant name]* to the best of your ability. We want the results of this study to represent **all** women, so including information about her is very important to us.

Please complete the enclosed *Form 33 - Medical History Update.* When you have completed the form, return it right away in the postage-paid envelope.

If you have any questions about the form, or need any help in filling it out, please call

_____ at _____. The information you provide about *[participant name]* will be kept confidential and her name will not be linked with data given to anyone other than the researchers in this study. Participation in this study is voluntary and you may refuse to answer any question on the form. However, it is very important that we have complete follow-up information on all participants to make sure that the results of the WHI are accurate and scientific.

We appreciate your help in the Women's Health Initiative. This is an important study designed to examine the health of a large number of women over a long period of time. The information you provide may help us find ways to improve the health of women for generations to come. Thank you for your support.

Figure 16.7
Postcard for Participants on No Follow-Up

WOMEN'S HEALTH INITIATIVE

1. Have you had any major health problems since we last saw you?
   ☐ No ☐ Yes → Please describe:_____
   _____

2. Is this address label correct?
   ☐ Yes ☐ No → Change to:_____
   _____

3. Are you interested in rejoining the Women's Health Initiative?
   ☐ No ☐ Yes

   I have questions, please call me at:_____
   Best times to call:_____

   Please call [CC phone number] or return this postcard to [CC address].

16.9 Follow-up Visits by Guest Participants

At times, it may be more convenient for a participant to have a follow-up visit conducted at a CC where she is not a participant (for example, if a participant is visiting a city where another CC is located at the time she is due for an annual visit). The following steps are needed at both the "visited CC" and the "home CC" when dealing with guest participants. Because of the added burden on the visited CC, these visits should only be done when the participant will not be returning home within a reasonable time period around her annual visit target date. However, if a guest participant "drops in" to a CC and wishes to complete a visit, the visited CC should make all efforts to accommodate her.

The visited CC should follow these steps:

1) Contact the participant's "home" CC to find out what tasks need to be collected at the visit, and to obtain the participant's WHILMA ID number.

2) Record the participant's full name and ID number on all forms.

3) If blood is collected, follow the instructions in *Volume 2, Section 11.4.1.2 - Mailing Instructions for Visiting Participants*. This section offers two options for handling blood specimens. The home and visited CCs should choose the option that is mutually agreeable to both of them. If the CCs choose the second option, the visited CC must contact McKesson to 1) give them the participant ID and the blood sample ID from the *Form 100 – Blood Collection and Processing*, and 2) let them know that the sample ID needs to be linked to the "home" CC in the McKesson database, even though the visited CC will be submitting the specimen as part of its routine blood shipment.

4) Send all forms to the home CC to be entered in WHILMA.

5) Instruct the participant to continue taking study pills from the bottle in her possession (if any). Determine whether the participant needs a new supply of pills and arrange for the home CC to mail a new supply to the participant at her temporary address, if appropriate. Instruct the participant to return her empty pill bottles and unused pills to the home CC at her next visit.

The home CC should follow these steps:

1) Dispense and mail a new supply of study pills to the participant's temporary address, if necessary.

2) When you receive the completed forms from the visited CC, create a new employee ID in WHILMA and call it "other CC". Use that employee ID number for all forms that are received from the visited CC.

16.10 Guidelines for Contacts with Participants' Survivors

These guidelines offer considerations, scripts, and activities for contacts with WHI participants' survivors (e.g., next-of-kin, spouses, or proxies) after a participant has died. These contacts may occur when you:

- try to contact the participant about routine activities (e.g., scheduling an annual visit)
- contact a participant's survivor to provide final medical history information (i.e., *Form 33/33D – Medical History Update*)—this usually occurs because CC staff have previously learned about the participant's death, either from survivors, notification by another participant, reading an obituary, or other sources (e.g., online databases, National Death Index)
- are contacted by a survivor to inform staff of the participant's death
- are contacted by a survivor in response to a routine communication (e.g., *WHI Matters* mailing)
- are contacted by a survivor in response to a written or voice mail expression of sympathy and/or request for final medical history information

16.10.1 WHI Expectations for Staff Contacts with a Participant's Survivor

Except within the scope of one's professional licensure, you are <u>not</u> expected to (nor should you) screen for the severity of a survivor's emotional response (e.g., depression, suicidal ideation) nor are you expected to treat that response. However, all staff should maintain a professional demeanor, convey understanding, and offer to end or postpone the interaction for an appropriate period of time. Refer to *Section 2.11.4.3 – Guidelines for Suicidal Ideation* for guidelines should you have concerns about a survivor's distress.

16.10.2 General Considerations for <u>All CC Staff</u>

Initial contacts with a participant's survivor. As outlined above, the initial contact with a participant's survivor may occur unexpectedly. If a CC learns of a participant's death via a written source (e.g., obituary, written notification), CC staff (e.g., Outcomes Coordinators) should exercise appropriate clinical judgment and consider waiting at least one month after the participant's death before initiating a contact for medical history information.

Generally, all CC staff who routinely make or respond to outside phone calls (e.g., receptionists) should be prepared for possible contacts with participants' survivors. The initial contact, whether initiated by a survivor or a CC staff person, at minimum, should begin with an expression of sympathy and gratitude for the participant's contribution to WHI. It may then be appropriate to refer the caller to an appropriate staff person who can begin the process of obtaining final medical history information. Even if the circumstances of the death are unusual (e.g., suicide), a general expression of sympathy is appropriate. Below is a sample script to use for these initial contacts:

Thank you so much for letting me know. I'm sorry to hear about _____ and offer my deepest sympathy. When did this happen? [Pause and document the date, as needed, for completing *Form 120 – Initial Notification of Death*.] *She was an important part of the Women's Health Initiative study over the years and we will miss her. You can be proud of the valuable contribution she has made to women's health care through her participation in this study.*

We would like to get some information to help complete her health records for the study. Is this a good time to talk with you or someone else about her health history or should I have someone call you at some other time?

Refer the caller to an appropriate staff person to begin an interview for *Form 33 – Medical History Update* (and/or *Form 33D – Medical History Update (Detail)*, as appropriate) or take down contact information and best time to call. Note that the caller may identify another person to give medical history information, ask the CC to wait for a period of time, express concern about providing such information, or refuse to provide this information. You should be prepared to respond to any of these scenarios.

Form 120 – Initial Notification of Death. Regardless of how the initial information about a participant's death is received, CC staff should initiate a *Form 120* and key-enter the available information in WHILMA so that future participant mailings will be stopped. The CC staff person who actually completes the *Form 120* may or may not be the one who had the initial contact with the survivor, based on local procedures. Depending on the circumstances of the initial notification, it may be appropriate to just enter an approximate date of death and who provided the information.

Sympathy note. Upon hearing of a participant's death, mail out a sympathy note or card to the next-of-kin or proxy. This note can contain hand-written text similar to the script above (e.g., expression of sympathy, recognition of participant's contribution to the study, setting the stage for future contact about participant's medical history). There are many good books available that offer examples of standard, but sensitive, sympathy notes to write.

Local resource list. The CC should be sure there is a short local resource list available that staff can offer to a survivor. Rather than trying to determine if a particular resource is needed or appropriate, CC staff should consider just generally offering it to each survivor (e.g., at the end of the contact—"*We have a list of resources that I can mail you."*). The resource list should include:

- a basic counseling resource that is relatively low cost or sliding scale
- health information resources (e.g., American Heart Association, American Cancer Society)
- crisis line (contact this resource first to make sure it is appropriate)
- additional resources, such as local/regional treatment sites (e.g., emergency rooms), bereavement/counseling services provided by religious organizations or a hospice group (which often offer services even if the participant did not use the hospice organization), web sites (e.g., http://www.aarp.com/griefandloss/, see "Understanding the grieving process" below)

Review this resource list and contact the printed phone numbers at least every 6 months to confirm that the list is still current.

Understanding the grieving process. There are many excellent resources (books, articles, web sites, professionals at your institution and in the community) available for learning more about bereavement and grieving. The most important point to remember is that there is no one "normal" response to loss and a person's response may have very little to do with the current interaction. Manifestations of grieving can take many different forms based on one's previous experience with loss, relationship with the participant, personality, and current life circumstances. A normal affect, anger, crying, withdrawal, denial, and a desire to talk things through are all possible responses. You are not expected to manage these responses beyond maintaining a professional demeanor, conveying understanding, and offering to end or postpone the interaction for an appropriate period of time. Some excellent resources related to grief and bereavement may be found on the World Wide Web, including:

- http://www.aarp.com/griefandloss/: The "Grief and Loss" website for the American Association of Retired Persons. Includes information about common reactions to loss and many other practical resources.
- http://www.centerforloss.com/library/centerforloss/contents.asp: From the Center for Loss and Life Transition in Colorado. This library of brief articles covers information for surviving family and friends as well as those who would like to help or understand the grief process.

CCs may also choose to provide some in-service training in this area.

16.10.3 Considerations for Staff Who Collect Medical History Information from Survivors

As described above in "WHI Expectations for Staff Contacts with Survivors," CC staff members who are responsible for obtaining participants' final medical history (*Form 33 – Medical History Update*) are not expected to make diagnoses about or to treat survivors' emotional health. However, Outcomes Coordinators or other staff who contact survivors for medical history information should have good interactional skills and a very basic understanding of the grieving process. There may be times when you feel very vulnerable to someone else's emotions (e.g., you have just experienced a loss). At these times, it may be appropriate to refer the contact to another CC staff person. Sometimes these contacts can extend longer than expected or just be emotionally draining. If you are the most appropriate person to make the contact, be sure that the call is made when you are not rushed, in a space where you will not be interrupted, and you are prepared operationally and emotionally.

Considerations for making the contact. When you are contacting a participant's survivor to obtain a participant's final medical history information, consider:

- Delay contact for at least one month after the participant's death (use clinical judgment), but avoid contacting survivors around the participant's birthday or on the same day of the death in subsequent months).
- Consider sending out a letter letting the survivor know you will be calling about the participant (so they can gather information) and then follow-up with the actual medical history update call a week or so later.
- Convey professionalism and understanding, particularly if the survivor wishes to delay or postpone the interview or becomes emotional (in which case, you should offer to postpone the interview; see *Section 2.11.4.2. – Special Situations*).
- Initially cover the elements of the basic script above.
- Ensure that the person you are talking with is the appropriate person from whom to obtain this information (*"Are you able to provide this information or is there someone else we should talk to?"*).
- Follow the basic interview script for *Form 33* (and *Form 33D – Medical History Update (Detail)*; see *Form 33* forms instructions in *Vol. 3 – Forms).*
- If the participant was in HRT and/or CaD, let the survivor know that we need all remaining WHI pills and bottles (including study pills remaining in pill organizers) returned to the CC. Offer to provide a mailer for this purpose.
- Make use of good interviewing skills (see *Section 2.11 – Interview Procedures*).
- If the survivor is angry, very reluctant to talk, or emotional, do not "blame" the person for his or her feelings or engage in debates about possible objections. You might say, *"It sounds like this is not the best time to talk. Thanks for your time today and I am sorry about your loss."* You will need to judge whether or not it is truly appropriate to offer to call back or whether such an offer might be met with an immediate refusal. In the latter case, instead of making the offer to call back, you might want to just end the call and postpone further contact for an appropriate amount of time. When you follow-up again, you may find some reluctant next-of-kin are now willing to talk.
- If encounters turn difficult, always keep in mind that you are doing the best you can and have all good intentions, even if sometimes you feel like you're not saying the "perfect" thing.
- Offer options for obtaining this information if there is ongoing resistance to doing the interview (e.g., mail or fax medical records or death certificate).
- If the participant is angry, reluctant or impatient about a single question or a series of related questions, cite "the office" or the "researcher." Blame the project for objectionable material, not the participant for being objectionable.

Some survivors may be willing to complete *Form 33/33D* by mail, but not over the phone or in-person. In that case, mail the *Form 33/33D* to the survivor. Follow-up for non-response to this mailing should be sensitive to the survivor's possible emotional needs to delay. If a participant's next-of-kin refuses to provide

this information or will not sign a medical release, note this information in the participant's progress notes. Your local Institutional Review Board (IRB) may have additional guidelines to consider. Refer to *Vol. 8, Section 2.2.4 – Reports of Death* for additional information on WHI procedures related to documenting and investigating a participant's death. *Vol. 2, Section 16.6 – Follow-Up by Proxy* also provides some guidelines on identifying and contacting proxies.

16.10.4 Family or Proxy Requests for Information*

Family members, friends, or designated proxies may ask for specific information about the participant who has died. Here is a possible script for responding to such requests:

We are committed to protecting our participants' confidentiality, so I hope you understand that we must follow careful guidelines and procedures before releasing information to people.

After offering this introductory explanation, provide the survivor with the specific guideline below based on the information requested.

- **Clinical trial treatment assignment:** HRT or CaD Treatment assignment may be made available to the legal next-of-kin upon written request during or after study close-out (procedures to be developed). The Dietary Modification is not a blinded trial, and treatment assignment information may be conveyed by staff who are not involved in outcomes ascertainment or adjudication.
- **WHI records**: A participant's blinded WHI records, including consent forms (not medical records obtained outside those generated by WHI) may be made available to the legal next-of-kin upon written request.
- **Results of blood analyses**: Only those analyses that were done at local laboratories (e.g., complete blood count at baseline and OS Year 3) may be made available to legal next-of-kin upon written request. Analyses done at central labs are not contained in the local databases and are logged centrally by an ID number only, so are not available to study participants or their next-of-kin.
- **Follow-up of physical exam findings (e.g., clinical breast exam, mammogram):** When participants have had abnormal or questionable measurements or exams, we often ask them to have further evaluation. Results of those follow-up exams (if performed by WHI) may be made available to the legal next-of-kin upon written request. The survivor may also request the name of the health care provider or clinic that performed outside exams.
- **Study information and findings:** Findings from the WHI are being published on an ongoing basis. Final results of the main study questions will be published after the study has closed, around 2007. The National Institutes of Health maintains a web page of study information and updates a list of selected publications at http://www.nhlbi.nih.gov/whi/index.html.

*Participant rights (even after death) dictate that information or records about her death may only be released to the legal next-of-kin. Although state laws may vary slightly, in general, legal next-of-kin is defined as:

- husband, if the participant was married
- children, if the participant was single and has children (unless the children are all minors)
- mother and father, if the participant was single (if mother and father are deceased, then her sisters and brothers are considered legal next of kin)
- other (if none of the above apply)

16.11 Guidelines for Participants With Cognitive Decline

These guidelines offer considerations and suggested strategies, not requirements, for working with WHI participants who have experienced some level of cognitive decline. These guidelines are meant to assist, not constrain, CC staff that must balance WHI procedural requirements with participants' capabilities and needs on a case-by-case basis. The ultimate purpose of these guidelines is to support the appropriate ongoing participation of WHI participants.

16.11.1 Identifying Potential Cognitive Decline in WHI Participants

Steady, progressive cognitive decline resulting in significant impairment is not a normal aspect of aging. Health and social problems among older persons are dynamic and may vary over time. Thus, cognitive functioning can vary over time. WHI participants will experience transient changes in their memory, thinking, and behavior depending on current life events and daily stresses, acute illnesses, or specific medications. Most of the time, these changes are troublesome but not disabling. Rarely, WHI participants will have progressive or profound changes in their cognitive status.

Because cognitive deficiencies can vary from minor to severe, your response to them can vary from minimal to substantial. Your response to cognitive decline should be based on a consideration of its severity and significance with respect to functioning. A thorough assessment of cognitive function is beyond the scope of WHI (though is included for WHIMS or WHISCA participants). However, a thoughtful approach to cognitive problems can help staff reduce barriers to WHI participation and identify care participants may need.

Procedures and tools for making an accurate evaluation of a participant's cognitive status and capabilities are complex and beyond the scope of these guidelines. Likewise, CC staff is not expected to formally assess a participant's cognitive status, except for the purpose of collecting data on current WHI forms (i.e., *Form 39 - Cognitive Assessment*). Responses to *Form 39* or other assessment tools are not necessarily an indication of the participant's competency to continue her participation in WHI, nor should WHI be providing primary health care or giving clinical advice based on such information.

CC staff will become aware of a participant's potential cognitive decline in many ways:

- while completing or reviewing *Form 39 - Cognitive Assessment* with an HRT participant, if she has difficulty with answering interview items
- by testing the subsample of participants who are enrolled in WHIMS or WHISCA
- while carrying out WHI tasks and procedures, if the participant seems confused or does not carry out the procedures (e.g., study pill taking) as appropriate
- based on information in medical records or health care provider reports provided to CC clinic staff
- based on information provided by the participant, a family member, or friend about a participant's cognitive changes or their consequences in her day-to-day life

CC staff is encouraged to discuss her/his concerns about a participant's cognitive decline with other appropriate CC staff and investigators to determine if additional information or specific accommodations should be considered.

16.11.2 Addressing Cognitive Decline Concerns

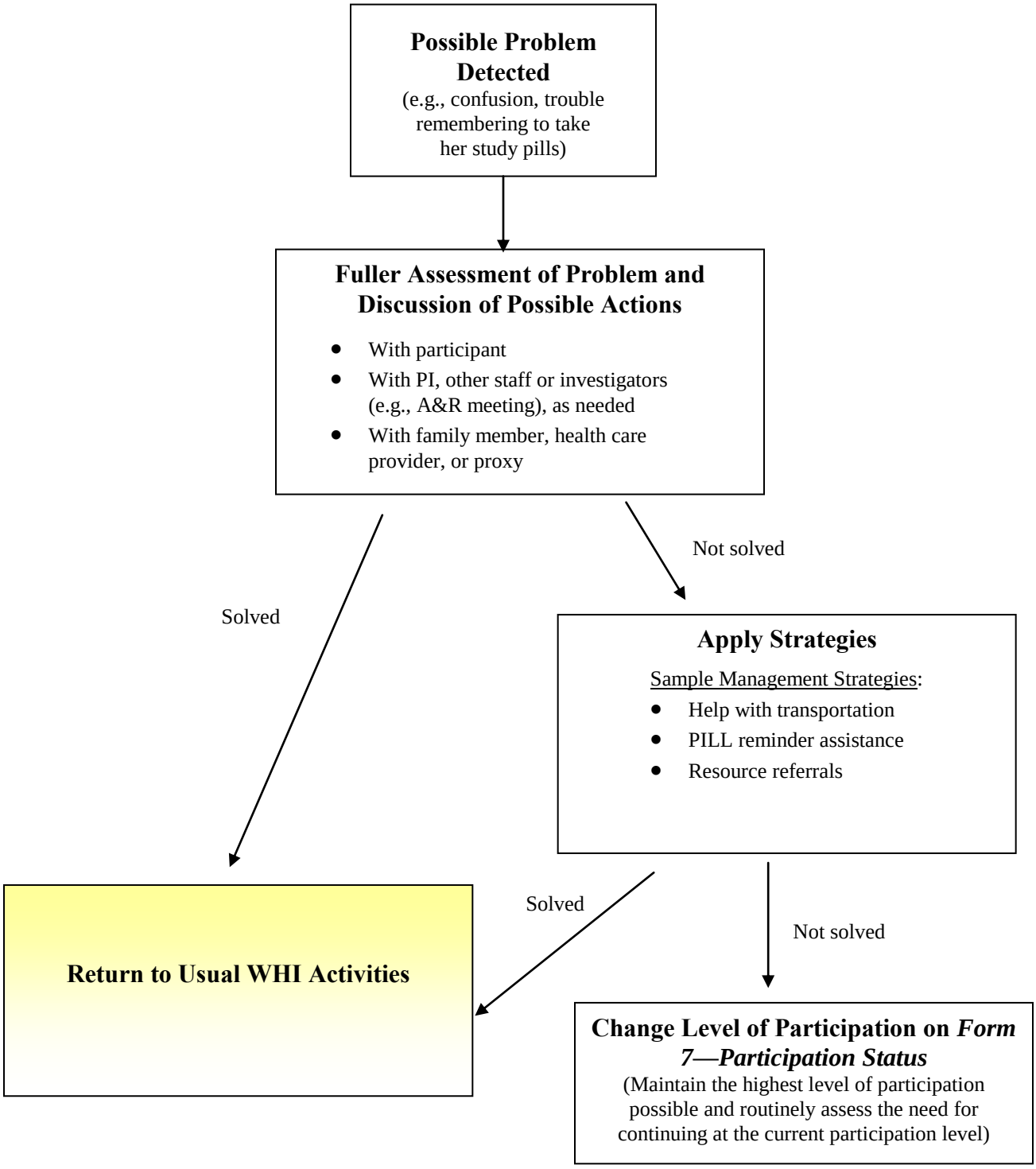
When addressing cognitive decline concerns, it is important to be comfortable with and have some skill in carrying out interactions with such participants. Matters will not be made worse by assessing cognitive function with participants, and it may help. CC staff without comfort or skill in this area should refer these participants to other appropriate staff or investigators. It is preferable, however, that CC staff proceeds with a thoughtful assessment and discussion with the participant.

The primary considerations when ***potential*** cognitive decline is identified include:

- the participant's safety while carrying out WHI activities
- the participant's ability to continue to provide appropriate data on WHI forms

The appropriate steps for addressing cognitive decline concerns are described below in *Figure 1*6.8 - *Algorithm for Addressing Cognitive Decline Issues*.

Figure 16.8 Algorithm for Addressing Cognitive Decline Concerns



16.11.2.1 Assess Specific Concerns

- With the participant (e.g., *Have you noticed any changes in your memory or thinking lately?*)

  In almost all circumstances, it is appropriate for CC staff to be straightforward with participants and directly confront the issue when it is detected (e.g., *At times today, you seem a little confused or forgetful* **or** *Is it getting harder to remember to take your study pills?).* If the participant identifies issues or circumstances that readily explain the confusion, a notation in her chart may be the only action warranted at this point. If the participant describes (or you note): 1) progressive and significant confusion or memory problems; 2) contacts with health care providers to evaluate her cognitive decline; or 3) tangential or irrelevant responses to your questions, additional steps may be appropriate.

- With your PI and other appropriate WHI staff or investigators

  A group discussion about the participant's situation (for example, at an adherence and retention meeting) can support a full consideration of both the issues and appropriate actions (see "Strategies" below) relevant to her WHI participation. For all participants, the discussion should also include plans for following up on the situation at a future meeting. For participants who are taking HRT or CaD study pills, this group discussion should include a careful consideration of the participant's ability to continue to safely follow the study pill regimen (alone or with assistance), monitor her own health and potential side effects, and complete safety tasks required for continuing on study pills. There may be times when a participant is in imminent danger. For example, immediate action may be warranted if study tests and procedures indicate a WHI alert (see *Vol. 1, Section 1 - Study Protocol and Procedures*), gross misuse of study medication is evident, or a report of domestic abuse is received. For DM Dietary Change participants, the group discussion might include the participant's expressed concerns about driving to the CC for group sessions, how the participant interacts in the group sessions, and how she completes self-monitoring tools and worksheets. Ultimately, the participants' safety and well being supercedes the need to keep people on their assigned regimens.

- With a family member, health care provider, or proxy

  Determine if they are aware of the participant's potential cognitive decline and what, if anything has been done to address this issue.

  It is important to obtain the participant's permission to make such a contact. (e.g., *I'm just a little concerned. Would it be okay if I talk with your [*family member, health care provider, or proxy*] to find out more about this?*). Document this discussion in the participant's chart. The person you contact may be knowledgeable about the participant's changes, aware of her participation in WHI, and able to support or suggest accommodations for her ongoing participation.

16.11.2.2 Carrying out Action Items

Carry out action items based on our discussion of this participant's situation.

- You may decide to continue her participation as before or implement one of the "Strategies" described below.

16.11.2.3 Changing Level of Participation

If concerns continue despite earlier actions, you may need to change her level of participation in WHI.

- If the participant's cognitive decline in WHI continues (e.g., a "temporary" cognitive decline does not resolve, the participant continues to be confused when responding to questions, study procedures or safety measures are not carried out appropriately), a change in participation status may be warranted. Appropriate changes may include stopping intervention, proxy follow-up, or other levels of participation. Discuss the ongoing situation with appropriate investigators and staff (as above) before completing *Form*

7 – Participation Status. Refer to *Section 17 – Retention* for information on addressing retention challenges and making changes in WHI participation levels.

16.11.3 Strategies for Managing a Participant's Cognitive Decline

There are many strategies to consider for managing cognitive decline concerns, depending on the participant's particular situation. These may include:

- Nurture close relationships with the participants, their family members, and their proxies throughout the study, even when no problems exist.
- Provide accommodations (e.g., transportation to the clinic if driving in traffic is upsetting and confusing to her, assistance with remembering to take study pills as in *Section 17 - Retention*) that will help her continue to fully participate in the study. It is important that staff directly confront and address with the participant her need for such accommodations (e.g., *I'm concerned that it may be dangerous for you to drive in heavy traffic.*).
- Provide the participant, her family member, or proxy with a referral to an outside provider, appropriate clinic, or other resource, if they want one. Most CCs already have local resource lists available.
- Actively involve a proxy or caregiver in helping the participant complete study procedures and forms. For more information about proxy procedures, refer to *Vol. 2, Section 16.6 - Follow-up by Proxy*. If the participant's routine procedures include pill taking in the HRT or CaD components, you should make a careful determination of the person's proximity to, ongoing relationship with, and willingness to safely support the ongoing activities of the participant. Note that *Form 60 - Food Frequency Questionnaire* is not to be completed by proxy.
- For participants who have documented or strongly-suspected cognitive decline, CCs will need to ask their local Institutional Review Boards (IRBs) about any requirements for re-consenting participants or reporting this information to an outside provider.
- Document ongoing assessment of the participant's cognitive status, as needed. Such informal assessments may be appropriate over the remainder of the study.

16.12 Procedures and Guidelines for HT/DM/CaD Pre-closeout Contacts

16.12.1 Introduction

The Steering Committee approved the HT Committee's recommendation to develop a pre-closeout plan focused on supporting the HT participant's transition to a personal health care provider at closeout. This document provides required procedures and guidelines that address this transition and support participant adherence and retention through closeout. These procedures are focused on pre-closeout activities for HT and CaD participants. Activities for DM Intervention participants are taking place during regular DM sessions.

Below is a brief overview of the pre-closeout activities:

- Requirements
  - Conduct a Transition Discussion (see below) with HT participants who are still taking study pills at either a visit or phone contact at least 6 months before the closeout contact (for safety reasons).
  - The "spirit" of all pre-closeout contacts should be congratulatory of the participants' achievements combined with a strong emphasis on preserving their commitment to the WHI and improving or maintaining their adherence until the very end of the study.[1] [*Congratulations… Making history… One more year… Still have unanswered questions… We need you!*]
- Recommendations:
  - Conduct Transition Discussion with all other HT and CaD participants.
  - Carry out Adherence and Retention Strategies (see below) with all HT and CaD participants.
- Materials
  - *Potential Questions and Answers* (for use in Transition Discussion and Adherence and Retention Strategies). This Q&A provides CC staff with appropriate responses to participant questions that may come up during this pre-closeout phase. Do not give this *Q&A* to participants; it is intended as a resource for CC staff only.
  - *Dear Dr. Doctor Letter and Information Sheet* (for use in Transition Discussion with HT participants)
  - *WHI Timeline/Milestones Charts* (for use with Adherence and Retention Strategies)

16.12.2 Transition Discussion

Identify those participants without a healthcare provider and discuss with them alternative strategies for healthcare follow up. If the participant has medical insurance, encourage her to find a provider. Use the *Potential Questions and Answers* as a resource during this discussion. If the participant does not have medical insurance, provide contact information for local healthcare agencies that serve uninsured and low income women. Steps taken to implement this part of the plan may vary by CC, depending on local resources. However, <u>all</u> CCs should:

- Identify participants without plans for healthcare after WHI.

[1] Critiques of the WHI E+P findings have often focused on E+P adherence (a summary measure that incorporates stop-intervention rates). Despite the fact that sensitivity analyses of the E+P data have confirmed our primary findings, we need to maintain the integrity of the WHI and prevent similar criticism of the E-Alone trial. Currently, only 53.2% of E- Alone participants are at 80% or more adherence, and the stop intervention rate for E -Alone is up to 40%. Therefore, we encourage you to incorporate these adherence and retention strategies into your pre-closeout activities. Don't let this potential opportunity slip by! We can still help some women realize that it is crucial to stay on study pills and to keep taking them regularly during these last visits.

- Create or update your list of local healthcare resources.
- Establish a link with social services to help uninsured participants seek care.

It is strongly recommended that you give HT participants the attached *Dear Dr. Letter and Information Sheet* to take to their healthcare provider (or offer to mail it directly to the provider, if the participant prefers). This material informs HT participants' providers about closeout, mentions the Follow-Up Study, and describes the provider's important role in partnership with the WHI.

Collaboration and partnership with local providers will be critical for supporting activities for the planned HT Follow-up Study. You could say, *"Healthcare providers across the country are watching the WHI very closely; they know that you're making medical history. We hope you'll give this information to your healthcare provider. It describes the important role that participants' providers have in WHI, particularly now that we're in our last critical year before closeout. If you'd like, we can mail this directly to your provider for you."*

16.12.3 Adherence and Retention Strategies

The second message celebrates the substantial contributions the participant has made to WHI in the past and emphasizes how important it is for her to continue in the trial on intervention, if possible, until the study is completed. The pre-closeout contacts offer excellent opportunities for reinforcing with participants the importance of their continued adherence and retention through to the Closeout Visit. Although this discussion may take place over the phone, the best strategy for promoting adherence and retention during pre-closeout contacts is to have an in-person discussion and to provide participants with "take-home" materials that illustrate and elaborate on the key messages.

In addition to the *Timeline/Milestones Charts* (see below for information and recommended talking points), additional materials you may want to have on-hand during this discussion include earlier updates and handouts ("DVT," "HERS," "2000 HRT Update," "2001 HRT Update," "Update on E+P Findings," "Osteoporosis Update", "Your Important Role …" —all available in the Public Folders), particularly those that correspond to the milestones. These handouts may be provided to participants or included in a notebook of relevant materials to have on-hand at the CC. The A&R Working Group is developing other materials suitable for including in a CC notebook; specifically, color PDF files of magazine covers and news articles related to the release of the E+P findings. CCs may also wish to enlarge the "WHI Timeline" or other charts to post in the CC.

Timeline/Milestones Charts

CCs are encouraged to provide HT and CaD participants with the *Timeline/Milestones Charts*. The "WHI Timeline," "HT Milestones," "CaD Milestones," and "Personal Milestones" (for participants to fill in their own milestones) can be used as visual aids when discussing the key adherence and retention talking points. These charts can be used to illustrate the history of WHI, the extended commitment the participant has made to the study, and the fact that we still have a few "milestones" to achieve.

"WHI Timeline" (with special text for DM participants)

- *This "WHI Timeline" shows the long and memorable history of WHI, from 1991—when the National Institutes of Health first began the project, to 1993—when recruitment started up, to 1998 when we last randomized participants into the Diet and Hormone Programs.* [Point to appropriate bubbles.]
- *You joined the study about here.* [Point to appropriate year.] *And we're now about here on the timeline.* [Point to appropriate date.] *You've been a very important participant in this timeline!*
- **For DM participants:** *Your role in the Dietary Study is very important. This is true for Comparison and Dietary Change participants. We need your continued help until the end of the study to find out if a low-fat dietary pattern that includes lots of fruits, vegetables, and grains lowers the risk of breast cancer, colorectal cancer and heart disease in postmenopausal women. The Hormone Program has*

shown how much WHI can contribute to the world's knowledge of women's health. Soon we will have the dietary results.

- *A lot has happened, and there are still some exciting events coming up!* [Closeout bubble.] *During this critical time, we hope you know how important it is to keep up your WHI contacts, and provide us with health information. It's also important for as many participants as possible to continue to take study pills regularly.*
- *We're certainly looking forward to sharing these future events—and the final WHI results—with you!* [Last bubble.]
- *What are your thoughts when you look at this timeline?* [Give the participant time to respond and then show her the "Milestones" chart(s).]

"HT Milestones"

- *This "Hormone Trials Timeline" chart shows the history of the study. You probably remember a lot of these milestones.*
- *We've been giving you pretty regular updates on the Hormone Trials, starting even before recruitment ended.* [End-of-recruitment bubble and several update bubbles.]
- *And then here's the BIG news that really hit the headlines!* ["WHI in the News" bubble.]
- *You can see that we're now heading into a critical time for WHI—we call it "closeout."* [Closeout bubble.] *We'll be scheduling closeout visits with all of our Hormone Trials participants during this time. At that closeout visit we'll collect some very important final information, we'll tell you more about your role in the Hormone Trials* [for E-Alone participants, you might mention that we'll be letting them know whether they were assigned to active or placebo pills]*, and we'll let you know about future follow-up for Hormone Trials participants.*
- *No matter which part of the Hormone Trials a woman has been in or whether she was assigned to take active or placebo pills, participants like you are making medical history.*
- *This has really been a long commitment on your part, and there are important milestones to come.*
- *Just as our milestones have been and continue to be a part of your life, you are a part of ours.* [Hand participant the corresponding "Personal Milestones" chart]

"CaD Milestones"

- *This "Calcium and Vitamin D Timeline" chart shows the history of the study. You probably remember some of these milestones.*
- *Even before the last participant was randomized to the study* [point to the appropriate bubble], *we were working on ways to help participants "hang in there" with taking pills* [point to the appropriate bubbles as you go along]*—we started having taste-tests so that women had a chance to try out study pills before they joined. And then we developed swallowable pills for those who wanted something different. Can you remind me, did you try both types?* [Give participant time to respond.]
- *You can see that we're now moving into a critical, "closeout" phase for WHI.* [Closeout bubble] *We'll be scheduling closeout visits with all CaD participants during this time. At that closeout visit we'll collect some very important final information, and we'll tell you more about your role in the Calcium and Vitamin D trial, including whether you were assigned to active or placebo pills.*
- *No matter which program women joined or whether they were assigned to take active or placebo pills, all WHI participants—like you—are making medical history.*
- *This has really been a long commitment on your par and there are important milestones to come.*

- *Just as our milestones have been and continue to be a part of your life, you are a part of ours.* [Hand participant the corresponding "Personal Milestones" chart]

"Personal Milestones" (HT or CaD)

- *We thought you might want to note your own milestones—things that have happened in your life while you have been a part of ours—things that have been important to you and your friends and family—achievements, new arrivals, local or national news events*.
- *I hope you'll write in the important events in your life. Are there are couple of milestones that occur to you right now?* [give the participant time to respond and then point to the last bubble] *But don't forget to leave that last "bubble" empty!*
- *We have some important milestones to come! We can't wait to hear about them, right?*

16.12.4 DM Adherence Motivational Postcard (for DM-I only)

The purpose of the *Dietary Adherence Motivational Postcard* is to support DM-I dietary adherence after the end of the Dietary Change Group sessions and until the close-out visit, for participants whose close-out visit is 3 or more months after their last Dietary Change session (10SU). The postcard provides a brief reminder of the WHI Dietary Study research question and asks the participant to continue to follow the WHI low-fat eating pattern through her close-out visit. The postcard also thanks the participant for her important role in the WHI Dietary Study.

The *DM Adherence Motivational Postcard* was shipped to the Clinical Centers in August. It is printed as a 2-sided card, folded in half, so that CCs can apply the participant address label and CC return address. (See *Figure 16.9* below.)

CCs are strongly encouraged to mail, or otherwise deliver, the postcard to DM-I participants whose close-out visit is 3 or more months after their last Dietary Change session (10SU). CCs may use the WHILMA Custom Data Extract System (CDE) to identify these participants and generate mailing labels. Refer to the WHILMA Upgrade Notes for the DM Adherence Postcard (Outlook Public Folders/All Public Folders/WHILMA Resources) for information about using the CDE to manage delivery of the *Dietary Adherence Motivational Postcard.*

Figure 16.9 – Dietary Adherence Motivational Postcard

Your Important Role in the WHI Dietary Study!

Even though your Dietary Change sessions have ended, we still need your help to complete the WHI puzzle and find the answer to the question we have been studying for many years:

Will an eating pattern low in fat and high in fruits, vegetables, and grains reduce the risk of breast cancer, colorectal cancer, and heart disease in postmenopausal women?

Please continue to follow the WHI low-fat eating pattern through your close-out visit.

Thank you for helping to complete the WHI puzzle!

16.13 WHI Close-out

16.13.1 CT Close-out

The CT close-out period begins on October 1, 2004 and ends on March 31, 2005. The CT Close-out visit is conducted for all CT participants, except those with a follow-up status of "no follow-up", "absolutely no contact", or deceased.

The purpose of the close-out visit is to:

- Complete collection of primary outcome data.
- Collect required study forms.
- Collect study pills.
- Collect adherence data from CaD participants.
- Collect adherence data from HT participants (if there are remaining study pills).
- Provide CaD participants with their treatment assignment.
- Recognize the participant's contributions to WHI.
- Present participants with the packet of close-out materials.
- Provide information and invite participation in the WHI Extension Study.
- Obtain signed consent from those willing to participate in the WHI Extension Study.
- Provide information and confirm participant's willingness to have her blood samples shared with non-WHI scientists at for-profit and non-profit organizations (Supplemental Consent).
- Obtain signed Supplemental Consent.

The close-out visit is important for celebrating the participant's participation in the study, encouraging the participant to join the WHI Extension Study, and to sign the Supplemental Consent. There are required tasks that need to be completed at the close-out visit; however, it is up to the CCs to conduct the visit based on available facilities and staffing. The close-out visit may be conducted as an individual visit, in a group setting, or as a combination of the two (for example, an initial group meeting with a limited number of participants and then meeting individually to further discuss and answer personal questions about the Extension Study Consent and Supplemental Consent).

16.13.1.1 Close-out Mailing Packet

One month to two weeks before the visit, mail the close-out mailing packet to the participants via first-class mail. Refer to *Table 16.4 – CT Close-out Mailing Packet Materials*, for materials to include in the close-out mailing packet.

An additional phone call reminder about the scheduled close-out visit may be made one to three days before the scheduled close-out visit.

16.13.1.2 Assemble Close-out Visit Materials Before the Close-out Visit

Print a follow-up visit information report, *WHIP0148,* for each participant. This report lists all the required WHI tasks to be performed at the close-out visit. Also print a copy of the current Personal Information Update.

Before the visit, assemble WHI folders with the materials that are included in the thank-you packet. Refer to *Table 16.5 – CT Thank You Packet Materials*, for a list of the materials to be included in the thank-you packet. To preserve blinding, the staff person who prepares the thank you packet for the participant and who may have access to the *WHIP9758 – CaD Treatment Assignment* should not be the same person who reviews and/or administers the *Form 33 – Medical History Update* to the participant at the close-out visit.

16.13.1.3 Conducting the Close-out Visit

During the close-out period, CCs are not required to collect tasks missed during contacts that were conducted before the close-out window (i.e., before Sept. 31, 2004), but may do so at the CC's discretion if staffing and time permit. Note: do not collecte a missed ECG and transmit it to Epicare after Sept. 31, 2004.

If participants cannot come to the close-out visit or complete all the close-out visit tasks, the priority of tasks to complete are listed below in the order of their priority and the order they should be done:

a) Collect the *Form 33 – Medical History Update* before providing CaD participants with their treatment assignment.
b) Collect *Form 33D – Medical History Update (Detail)* as needed.
c) Collect the Release of Information.
d) Provide CaD participants with their treatment assignment letter.
e) Date the *Form 28 – Treatment Assignment – CaD* with the date the participant is unblinded.
f) Obtain the WHI Extension Study Consent.
g) Obtain the Supplemental Consent.
h) Complete all other close-out tasks.

16.13.1.4 Close-out Visit Procedures

A suggested scenario for the close-out visit is described below. Each CC can organize the flow of the close-out visit to fit its needs as long as the visit includes the following activities.

a. Reception

When the participant arrives for her close-out visit, have her check in with the receptionist. The receptionist should:

- Warmly greet the participant by name and welcome her to her close-out visit.
- Ask the participant if she has brought her completed forms and study pill bottles (empty or not) and pill organizers as appropriate. Collect and attach the returned forms to the top of her participant file. If she has not remembered to bring the forms, provide her with a replacement set and ask her to complete them while she is waiting.
- State the approximate time needed to complete the visit and explain the visit flow.
- Indicate a comfortable place in the reception area where the participant may wait.
- Notify the clinic staff that the participant is waiting.
- Try to limit participant's wait to no more than 10 minutes before she is seen by an interviewer.

b. Questionnaire Review

Review the returned self-administered questionnaires. Identify missing pages and remind the participant to complete them. Ensure a participant barcode label is on the front page of each completed form in the designated place.

There is no close-out contact flag in WHILMA for forms that are collected at closeout. The close-out contact is identified by the *Form 33* that is collected during the close-out period October 1, 2004 through March 31, 2005. This means that if a *Form 33* is completed by the participant before her close-out visit, the *Form 33* must be reviewed with the participant and the "Date Form Finished" question at the end of the form updated with the date of the actual close-out contact. There is no need to update the contact date (the "date received"); the finished date will be used to determine whether the data was collected within the close-out period.

- *Form 33 – Medical History Update.* If the participant indicates she has had any events or conditions on *Form 33 – Medical History Update* that necessitate more detailed information for an outcomes investigation, ask her to complete *Form 33D – Medical History Update (Detail)* (see *Form 33* instructions for the algorithm that triggers a *Form 33D* and *Vol. 8 – Outcomes, Section 2 – Ascertainment*).
- *Form 37 – Thoughts and Feelings, Ver. 6.*

- *Personal Information Update.*
- *Form 55 – Estrogen-Alone Survey, Ver. 2* (only E-Alone participants who were taking study pills at the time the intervention stopped in March 2004).

c. Release of Information

Ask the participant to sign several new copies (2-3) of your CC's *Release of Information*. Explain to the participant that these new forms will replace the last ones she signed.

d. Required Forms to Complete at the Visit

- Complete *Form 85 – Mammogram* (for E-Alone and E+P participants who had their last annual visit between October 1, 2003 and March 2004).
- Administer *Form 10 – HRT Management and Safety Interview* (for E-Alone participants requiring their second *Form 10* since stopping intervention).
- Administer *Form 17 – CaD Management and Safety Interview* (CaD).

Note: *Form 10A* and *17A* may be used throughout the close-out period even though historically, *Form 10A* and *17A* were only used for semi-annual contacts for participants with good adherence. Questions 14–16 (*Form 10/10A*) and 10-16 (*Form 17/17A*) do not need to be answered if the participant stopped intervention before the close-out visit.

e. Adherence to CaD Study Pills – *Task 951* (also for HT if not already collected)

Collect the participant's study pill bottles and pill organizers. Assess the participant's adherence to taking the study pills (this may be an actual or estimated adherence collection). Update any estimated adherence collections with actual adherence (weight).

f. CaD Treatment Assignment

- Complete *Form 28 – Treatment Assignment – CaD.* Complete and date this form on the day the participant is provided her treatment assignment.
- Perform the CaD Unblinding task in WHILMA and print two copies of the report.
- Provide the participant with a copy of *WHIP9785 – CaD Treatment Assignment* and place the second copy in her chart.

g. Thank You Packet

Give the participant the prepared close-out thank-you packet and thank her for her participation. Refer to *Table 16.5 – CT Thank You Packet Materials* for materials to be included in the close-out packet. The Dietary Study materials to be included in the CT thank you packet are described below

- **WHI Dietary Study Summary (for DM-I and DM-C)**

The *WHI Dietary Study Summary* is designed to a) help Dietary Change participants make choices by seeing the similarities and differences between the goals of the WHI Dietary Study and National Dietary Guidelines for the public and b) to provide Comparison participants a brief orientation to the WHI eating pattern without implying WHI recommendations or reviewing the low-fat dietary pattern in any detail.

Talking Points for Staff:

The WHI Dietary Study Summary provides a snapshot of what the WHI low-fat eating pattern looked like. The first page of the handout compares the goals of the WHI Dietary Study to National Dietary Guidelines for the Public. The second page includes two sample menus that provide a few examples of food choices that women in the Dietary Change group made to eat low-fat. This handout does not provide recommendations about what to eat.

For information about managing participant questions about the Dietary Study materials, refer to *Troubleshooting Participant Questions about the Dietary Study Materials* below.

- **WHI Dietary Study Frequently Asked Questions (for DM-I and DM-C)**

The *WHI Dietary Study Frequently Asked Questions* is designed to address DM participant questions about a) the WHI low-fat eating pattern and b) how to proceed until DM study results are known.

Talking Points for Staff:

We recognize that you may have questions about the WHI Dietary Study. The WHI Dietary Study results will be available in early 2006. In the meantime, these "WHI Dietary Study Frequently Asked Questions" provide answers to some frequently asked questions. The first page gives information about the WHI Dietary Study design. On the second page, you'll find information about when the Dietary Study results will be available. The last page gives a reminder to see your personal health care providers (including a registered dietitian) when seeking dietary advice. If you're interested, the last page also describes where to find more information about nutrition.

For information about managing participant questions about the Dietary Study materials, refer to *Troubleshooting Participant Questions about the Dietary Study Materials* below.

- **Troubleshooting Participant Questions about the Dietary Study Materials.**

If a participant asks about when Dietary Study results will be available:

Point the participant to the *'How and when will I learn if...?'* question on the second page of the *WHI Dietary Study Frequently Asked Questions*.

WHI scientists will compare disease rates between the Dietary Change and Comparison groups after all participants have completed their close-out visit (March 31, 2005). This comparison will let us see if the WHI eating pattern reduced the risk of developing breast cancer, colorectal cancer, and heart disease. We will mail the study results to you after all the data have been analyzed. This will be in early 2006.

If a participant asks about what she should eat:

Point the participant to the *'What should I eat?'* question on the third page of the *WHI Dietary Study Frequently Asked Questions*. Avoid offering dietary advice.

Your personal health care providers, including a registered dietitian, can offer guidance about an eating pattern that is right for you. Contacting your personal health care providers for dietary guidance is particularly important if you have a diet-related health condition such as diabetes, heart disease, or are above or below a healthy weight. The Dietary Summary included in your close-out packet provides a snapshot of current national dietary guidelines for the public and how they compare to the goals of the WHI Dietary Study. There are many similarities between the two eating patterns. When the WHI Dietary Study results become available in early 2006, you can also consider them in light of your personal needs to further guide your food choices.

If a participant asks about where to find more information about nutrition:

Point the participant to the *'If I want more information about nutrition, where can I find it?'* question on the third page of the *WHI Dietary Study Frequently Asked Questions.* Do not offer dietary advice.

The American Dietetic Association (ADA) is the nation's largest organization of food and nutrition professionals. The ADA has a Consumer Hotline (1-800-366-1655) where you can

listen to brief pre-recorded nutrition messages or get help finding a registered dietitian in your local area. You can find additional food and nutrition information at the ADA website (www.eatright.org). The U.S. government has many health-related resources. For example, the www.healthierus.gov website offers information about a variety of nutrition topics such as healthy eating, food label reading, the USDA Dietary Guidelines for Americans, and the 5 A Day for Better Health program.

h. Consents

Explain and obtain consent for the WHI Extension Study and the Supplemental Use of Specimens. See *Vol. 2, Section 16.14 – WHI Extension Study and Supplemental Use Consent* for details on collecting this consent.

i. CT BMD Scans at Bone Density (BMD) Sites

All BMD cohort CT participants at the three BMD CCs will receive an AV9 BMD or a close-out BMD (if they have not yet had the AV9 BMD). If a participant has had an AV9 BMD within 12 months of the close-out visit, an additional BMD is not required at close-out. A urine sample or height measurement is not required at the close-out visit. Refer to *WHIP0148 – Follow-up Visit Information* to determine if a BMD is required.

j. Exit Interview

Spend a few minutes with the participant to discuss her future involvement with WHI if she is transitioning to the Extension Study. If she has signed the Extension Consent, explain to her when she may expect to receive the first packet of materials for the Extension Study. If she has declined signing the Extension Consent, make sure she is thanked for the participation that she has maintained and celebrate with her the fact that she has made history with a large group of women who have contributed a wealth of information to women's health. Refer to the March 22, 2004, WHI Times for tips for "Saying Goodbye" to participants.

Make sure that the participant is aware that:

- Her participation to WHI has been and remains invaluable.
- She should contact the CC with any questions or concerns that she may have in the future.

Participant retention may be promoted by sending a personalized thank-you card within a week of the visit.

16.13.1.5 Activities for Participants Who Do Not Come to the Close-out Visit

Participants who do not come to the CC for a close-out visits (e.g., "no shows" or "no visit" follow-up) may be contacted by phone or mail to collect the priority tasks. CCs should ensure a thank-you packet is mailed to the participant who does not attend the close-out visit (except those participants with a follow-up status of "no mail", "absolutely no contact", or "deceased").

16.13.1.6 Ancillary Study Tasks at Close-out

Refer to the appropriate ancillary study coordinating center for details on ancillary study tasks required at close-out.

Table 16.4 – CT Close-out Mailing Packet Materials

	CT Documents	Mail	Purpose	Source Location	Title in Public Folders	Manual
1	Close out visit appt. reminder (required)	All	CC includes as cover memo for mailed packet; includes checklist on second page	CC Prints Close-out/Packets/CT Close-out mailing packet	Close-out visit Appointment Reminder.doc	*Vol. 2, App. E.7.1*
2	*Form 33 – Medical History Update* (required)	All	A routine data collection form	CCC/GPO prints	-	*Vol. 3*
3	*Form 37 – Thoughts and Feelings* (required)	All	A routine data collection form	CCC/GPO prints	-	*Vol. 3*
4	*Personal Information Update* report (required)	All	A routine data collection form	CC prints from WHILMA	-	-
5	*Form 55 – Estrogen-Alone Survey* (E-alone) (required for participants on E-Alone at the time E-Alone intervention was stopped)	E-alone	A routine data collection form	CCC/GPO prints	-	*Vol. 3*
6	Cover letter – Extension Study Consent - (non-HT) (required)	Non-HT	A cover letter to attach to the Extension Study consent for non-HT participants	CC Prints Close-out/Packets/CT Close-out mailing packet	Cover letter – CT Pre-visit (non HT) Extension Study Consent.doc	*Vol. 2 App. E.7.2*
7	Extension Study Consent – (non-HT) (required)	Non-HT	Used to obtain informed consent for Extension Study (place a participant barcode label on both copies)	CC Prints Close-out/Packets/CT Close-out mailing packet	Extension Study Consent (non HT).doc	*Vol. 2 App. E.7.3*
8	Cover letter – Extension Study Consent - (HT) (required)	HT	A cover letter to attach to the Extension Study consent for HT participants	CC Prints Close-out/Packets/CT Close-out mailing packet	Cover letter – CT Pre-visit (HT) ExtensionStudy Consent.doc	*Vol. 2 App. E.7.4*
9	Extension Study Consent – (HT) (required)	HT	Used to obtain informed consent for Extension Study (place a participant barcode label on both copies)	CC Prints Close-out/Packets/CT Close-out mailing packet	Extension Study Consent (HT).doc	*Vol. 2 App. E.7.5*
10	Cover letter – Supplemental Consent (required)	All	A cover letter to attach to the Supplemental Consent	CC Prints Close-out/Packets/CT Close-out mailing packet	Cover Letter – CT Pre-visit Supplemental Consent.doc	*Vol. 2 App. E.7.6*
11	Supplemental Consent (required)	All	Used to obtain informed consent for Supplemental consent (place a participant barcode label on both copies)	CC Prints Close-out/Packets/CT Close-out mailing packet	Supplemental Consent.doc	*Vol. 2 App. E.7.7*

Table 16.5 – CT Thank you Packet Materials

	CT Documents	Visit	Purpose	Source Location	Title in Public Folders	Manual
1	Thank you packet cover letter (required)	All	CC includes as the cover letter for the thank-you packet	CCC/GPO prints Close-out/Packets/CT Thank you packet	Cover letter – CT Thank you packet.doc	*Vol. 2 App. E.7.8*
2	PI thank-you letter (optional)	All	Individualized thank-you letter signed by PI	CC Prints Close-out/Packets/CT Thank you packet	Cover letter – PI Thank you.doc	*Vol. 2 App. E.7.9*
3	CT Close-out Newsletter ("WHI Matters") (required)	All	A newsletter focusing on the legacy of WHI	CCC/GPO prints Close-out/Packets/CT Thank you packet	CT Close-out Newsletter.pdf	-
4	Health Screening Guidelines handout (required)	All	General health screening guidelines for women over 50	CCC/GPO prints Close-out/Packets/CT Thank you packet	Health Screening Guidelines.doc	*Vol. 2 App. F.5.1*
5	Certificate of Appreciation (required)	All	Personalized certificate commemorating woman's participation	CCC/GPO prints template, CC adds participant name Close-out/Packets/CT Thank you packet	Certificate of Appreciation.pdf	*Vol. 2 App. F.5.2*
6	Incentive: mirror/sewing kit (required)	All	CT incentive	CCC	-	-
7	Incentive: jar gripping opener (required)	All	CT/OS incentive	CCC	-	-
8	WHI Dietary Study Summary (required for DM, optional for others)	DM	A handout for DM-I and DM-C participants	CCC prints for DM only; CC prints for others Close-out/Packets/CT Thank you packet	DM Summary.doc	*Vol. 2 App. F.5.3*
9	WHI Dietary Study Frequently Asked Questions (required for DM, optional for others)	DM	A handout of FAQs for DM-I and DM-C participants	CCC prints for DM only; CC prints for others Close-out/Packets/CT Thank you packet	DM FAQ.doc	*Vol. 2 App. F.5.4*
10	CaD Fact Sheet (required for CaD, optional for others)	CaD	A handout about CaD	CCC prints for CaD only; CC prints for others Close-out/Packets/CT Thank you packet	Calcium Fact Sheet.doc	*Vol. 2 App. F.5.5*
11	WHIP9758-CaD Treatment Assignment (required)	CaD	Unblinding letter for CaD participants	CC prints from WHILMA Close-out/Packets/CT Thank you packet	WHIP9758-CaD Treatment Assignment.pdf	-
12	WHI Folder	All	Holds thank you packet materials	CCC/GPO prints	-	-

16.13.2 OS Close-out

Close-out data are collected from OS participants using procedures similar to those used during the annual OS follow-up. Data collection attempts by mail (Contacts 1-4) are conducted by the CCC (see *Vol. 2, Section 16.13.2.2 – CCC Responsibilities for OS Close-out* for details). For participants who do not respond to the mailed contacts, data collection attempts by telephone are conducted by the CCs (see *Vol. 2, Section 16.13.2.3 – CC Responsibilities During OS Close-out (Required)* for details). OS close-out mailings begin April 2004 (first Contact 1s) and end in April 2005 (final Contact 4s). Follow-up phone calls to collect *Form 33 – Medical History Update* from non-respondents and to collect *Form 33D – Medical History Update (Details)* can continue through July 2005.

All OS participants, except those who are deceased or on "absolutely no contact" status should receive a close-out packet, since it contains extra information and expresses appreciation for her participation. The CCC sends mailings to all OS participants except those with a follow-up status of "no mail", "proxy", or "absolutely no contact". For participants on "no mail" or "proxy" follow-up, or with undeliverable addresses, the CC should make every attempt to provide them with the close-out materials. The forms may be completed at any time during the close-out period.

The purpose of the OS close-out packet is to collect close-out data, thank the participant for her years of participation, provide summaries of study results to date, and provide an introduction to the "WHI Extension Study". See *Table 16.7 – OS Close-out Mailing Packet Materials* for materials included in the close-out packet.

All CCC mailed packets are sent third-class (bulk) mail in a mailing envelope printed with the CC's return address, the CCC's bulk mailing permit number, and a request for notification of change of address.

Table 16.6 – Timing of OS Close-out Data Collection shows the approximate dates for completion of OS close-out data collection by enrollment month.

Table 16.6 – Timing of OS Close-out Data Collection

Enrollment month	Contact 1 mailing mo(CCC)	Contact 3* mailing mo (CCC)	Contact 4 mailing mo (CCC)	Phone follow-up (CC)	Approx 33D collection (CC)
June (any year)	April 04	July 04	Sept 04	Nov 04	May 04
July	May 04	August 04	Oct 04	Dec 04	June 04
August	June 04	Sept 04	Nov 04	Jan 05	July 04
Sept	July 04	Oct 04	Dec 04	Feb 05	Aug 04
October	August 04	Nov 04	Jan 05	March 05	Sept 04
November	Sept 04	Dec 04	Feb 05	April 05	Oct 04
December	Oct 04	Jan 05	March 05	May 05	Nov 04
January	Oct 04	Jan 05	March 05	May 05	Nov 04
February	Nov 04	Feb 05	April 05	May/June 05	Dec 05
March	Nov 04	Feb 05	April 05	May/June 05	Dec 05
April	Dec 04	Feb 05	April 05	May/June 05	Jan-July 05
May	Dec 04	Feb 05	April 05	May/June 05	Jan-July 05

*Contact 2 (a thank you/reminder postcard) was discontinued several years ago.

16.13.2.1 Timing of the "Regular Annual OS Mailing" During the Year Preceding Close-out

Mailings and related activities during the year prior to close-out are conducted on the usual schedule. That is, the last pre-closeout Contact 1s are mailed in March 2004. Contact 3s and 4s for these women occur in June 2004 and August 2004. CC phone follow-up with these participants should occur in October 2004.

Forms that were mailed out as part of the previous year's mailing (i.e., not a close-out mailing) and are received within the close-out window will NOT be counted as the close-out mailing. For example, if an AV8

set of forms is mailed in March and is received at the CC in April, it will count as an AV8, not as a close-out form. That participant would receive a close-out packet toward the end of the close-out year.

To help distinguish close-out forms from pre-close-out follow-up forms (which CCs will continue to receive through approximately September 2004), a "CO" for close-out appears on the forms' participant ID labels. The *Form* 33 will have 2 labels: 1) a date label with the date of the last *Form* 33, OS contact number (1, 3, or 4), and corresponding barcode CO (for close-out) and participant ID; and 2) a participant ID label with participant name, participant ID, and barcode, CO (for close-out) and OS contact number. To help distinguish which participants are non-respondents needing follow-up to the close-out mailing, a "close-out flag" appears on *WHIP1206 – OS Members Needing CC Follow-up*.

16.13.2.2 CCC Responsibilities for OS Close-out

The CCC is responsible for the printing (through the GPO), assembly, and outgoing postage costs for the mailed close-out data collection contacts. The mailed contacts include:

- An initial mailing of the entire close-out packet (Contact 1)
- A second mailing of the entire packet (Contact 3)
- A third mailing of the entire packet (Contact 4)

Spanish language versions of the contact materials are mailed to participants whose primary language is Spanish, as indicated by the "Preferred Language" flag on the Contact Information Screen in WHILMA.

- **First Mailing of the Close-out Packet (Contact 1)**

  Initial mailings to participants start in April 2004. Contact 1 mailings are sent two months prior to the enrollment anniversary (i.e., those mailed in April are to women who enrolled in June). To allow adequate time for completion of *Form 33D* and outcomes processing, the close-out mailing year for Contact 1 is shortened from 12 months to 9, that is, the mailing year ends in December 2004 instead of March 2005 (see *Table 16.6 – Timing of OS Close-out Data Collection*). All participants will receive a mailing during the close-out period; the last 5 months worth of Contact 1 mailings (i.e., January – May mailings) will be sent October – December 2004.

- **Second and Third Mailing of the Entire Follow-up Packet (Contact 3 and 4)**

  A second complete follow-up packet (Contact 3) is mailed the month after the participant's enrollment anniversary month (three months after the mailing of Contact 1) to those participants who did not respond to the first mailing (i.e., those who did not complete and return the form sent in Contact 1 and for whom the CC has not indicated receipt in WHILMA). The final few months of the close-out period (i.e., January – May) will be shortened to two months (January and February). The last Contact 3 mailings will be sent in February 2005 (see *Table 16.6 – Timing of OS Close-out Data Collection*).

  The third packet (Contact 4) is mailed three months after the enrollment anniversary month (two months after Contact 3) to those participants who have not completed and returned the forms sent during earlier contacts and for whom the CC has not indicated receipt in WHILMA. The last Contact 4 mailings will be sent in April 2005 to allow for adequate time for completing of *Form 33D* and outcomes processing (see *Table 16.6 – Timing of OS Close-out Data Collection*).

16.13.2.3 CC Responsibilities During OS Close-out (Required)

The CCs have several responsibilities during the close-out mailing of Contacts 1-4. These responsibilities, which are similar to those used during OS annual follow-up, consist primarily of:

- Updating WHILMA to reflect that *Form 33* has been completed and returned. The procedures for processing returned packets during the close-out period are identical to those used during annual follow-up. See *Vol. 2, Section 16.5.2.1 – Processing Returned Packets (Contacts 1-4) (Required)* for procedures.

- Making address corrections as soon as they become available. See *Vol. 2, Section 16.5.2.2 – Making Address Corrections (Required).*
- Completed forms are returned directly to CCs in the business reply envelopes provided in the packet. Clinical Centers are responsible for paying the postage for these completed, returned forms.
- Running monthly reports from WHILMA to identify participants who do not respond to the mailed contacts (see *Vol. 2, Section 16.13.2.4 – CC Data Collection for Non-Respondents to OS Close-out Mailings (Required)* for more details). This activity will continue through July 2005.
- Follow up with non-responders listed on *WHIP1206* to collect *Form 33s.* See *Vol. 2, Section 16.13.2.4* below.
- Continue attempting to locate and collect *Form 33* from all participants listed on *WHIP1591 – Participants Who Are Lost-to-Follow-up*, as per current procedures (see *Vol. 2, Section 17.3 – Locating "Hard to Find" Participants*).
- Collect *Form 33D – Medical History Update (Details)* data by phone or mail consistent with current procedures. Collection will start upon receipt of the first *Form 33*, around May 2004, and will continue through collection of the final *Form 33* in July 2005.

16.13.2.4 CC Data Collection for Non-Respondents to OS Close-out Mailings (Required)

During close-out, CCs are responsible for collecting *Form 33 – Medical History Update* on those participants who have not responded to the close-out mailings. CCs are required to follow-up with all non-respondents during close-out, regardless of their follow-up year. This includes those on "no mail", "proxy" or "no follow-up", and those with an undeliverable address. If a participant does not have a completed *Form 33* in WHILMA by the seventh month after the mailing of Contact 1 (i.e., five months after her enrollment anniversary), staff should initiate telephone contacts to collect the data. This is done through telephone attempts to reach the participant or proxy to collect the data. Non-respondents needing follow-up data collection are listed on *WHIP1206 – Members Needing CC Follow-up* (see *Vol. 2, Section 16.5.2.3* for WHILMA procedures). See *Vol. 2, Sections 16.5.3.1 – Telephone Contact to Ascertain Correct Address and to Collect Medical history Update* and *16.5.3.2 – Mail/Phone Contact to Trace Participant and/or Collect Medical History Update from Proxy* for details on collecting data from non-respondents.

If a participant did not receive a mailed packet (e.g., because she had an "undeliverable address" or is on "no mail" or "proxy"), CCs are encouraged to send her a copy of the newsletter, a certificate of appreciation, and a thank you bookmark following the phone contact, even if she does not agree to complete the *Form 33*. A small supply of these close-out items have been provided to CCs for this purpose. The report for personalizing the certificate of appreciation (*WHIP9757*) is included in the June 2004 WHILMA upgrade.

Telephone calls to non-responders, whose first mailings were sent in December 2004, may be made one month after the Contact 4 mailing, rather than waiting for two months. To get a list of these respondents, run *WHIP1206* at 5 or 6 months after the first mailing (rather than the default of 7 months) to ensure adequate time for follow-up. For these participants, *WHIP1206* should be run in May or June 2005, following the Contact 4 mailing in April.

16.13.2.5 OS BMD Scans at Bone Density (BMD) Sites

AV9 BMD scans can be scheduled up through September 30, 2004. No BMD scans should be scheduled after October 1, 2004 (the start of CT close-out visits). Starting in April, 2004, the CCC will be mailing forms to the bone density participants, instead of having them mailed by the CCs.

Table 16.7 – OS Close-out Mailing Packet Materials (Mailed by CCC)

	OS Documents	CCC Mails	Purpose	Source Location	Title in Public Folders	Manual
1	Thank-you cover letter – contact 1 (required)	All	Included as the cover letter for packet (contact #1)	CCC/GPO prints Close-out/Packets/OS Close-out Mailing Packet	Cover letter – Oscovfin2.doc	-
2	Thank-you cover letter – contact 3 -4 (required)	All	Included as the cover letter for packet (contact #3-4)	CCC/GPO prints Close-out/Packets/OS Close-out Mailing Packet	Cover letter – Osfincov34.doc	-
3	*Form 33 – Medical History Update* (required)	All	A routine data collection form	CCC/GPO prints	-	-
4	*OS Follow-up Questionnaire* (required)	All	A routine data collection form corresponding to participant's follow-up year: Form 146 and Form 149 for AV6 Form 147 for AV7 Form 148 for AV8 No Form for AV9 or AV10	CCC/GPO prints	-	-
5	OS Extension Study announcement ("Breaking News") (required)	All	Announcement of the Extension Study for OS participants	CCC/GPO prints Close-out/Packets/OS Close-out Mailing Packet	WHI Extension Study Announce.doc	-
6	Certificate of Appreciation (required)	All	A personalized certificate of appreciation	CCC/GPO prints template and CCC adds participant name Close-out/Packets/OS Close-out Mailing Packet	Certificate of Appreciation.pdf	*Vol. 2 App. F.5.2*
7	Close-out Newsletter (required)	All	OS newsletter describing OS participants as a group and informing them of planned mailing of study results	CCC/GPO prints	-	-
8	Thank-you gift: Magnifying bookmark – contact 1 (required)	All	OS thank-you gift (for contact 1)	CCC	-	-
9	Incentive: Jar gripping opener contact 3-4 (required)	All	OS/CT thank-you gift (for contacts 3-4)	CCC	-	-
10	#2 pencil (required)	All		CCC	-	-
11	Business reply return envelope with CC address (required)	All		CCC	-	-

16.13.3 Proxy Close-out (CT and OS Participants)

For CT and OS participants on proxy follow-up, contact the proxy by phone or mail to collect the close-out *Form 33* and, if necessary, *Form 33D*. If the *Form 33* is sent by mail, include a thank you letter letting the proxy know that the study is coming to an end, as well as any supplemental information that the proxy might be interested in seeing and/or sharing with the participant, such as the CT or OS close-out newsletter, the health recommendations, and the thank you gift. If the forms are collected by telephone, follow the call with a thank you packet.

If the participant is in the CaD Study and is on active intervention status, contact the proxy and let him/her know that the participant should stop taking her study pills.

There are no study-wide plans for providing deceased participants' proxies with close-out information, though Clinical Centers may send this information to proxies (depending on individual or family circumstances) if they wish.

If a CC sends information to a proxy, enclosing a cover letter acknowledging the special role of proxies is recommended.

16.13.4 Close-out Events (CT and OS Participants)

Centers may choose to plan group close-out events for participants. As opposed to group visits, these events are generally celebratory in nature. As long as the goal is participant appreciation, and activities and messages are neutral, all participants in the CT and OS may attend together. In accordance with the Project Office (12/3/03 memo from the Project Office, posted in Public Folders/Close-out folder), close-out participant events may be billed to the contract when reasonable expenditure of costs is likely to result in proportional relative benefit toward fulfillment of contractual objectives. The NHLBI concurs that small expenditures per participant may be incurred for CT participants to encourage retention. No further NHLBI approval is required for costs not exceeding $5.00 per CT participant. Any event for CT participants should have an opportunity for the dissemination of technical information, such as study findings. For OS participants, an informational meeting without incentives requires no further NHLBI authorization. Centers are encouraged to work with local businesses and community organizations to enhance the funds available for events or incentives. Real or apparent endorsements must be avoided in all cases.

16.13.5 Outcomes

One purpose of the close out contact is to complete ascertainment of primary outcome data, including collection of *Form 33* and *33D* (if required), procurement of medical records documentation and adjudication. It is not necessary to collect missing *Form* 33s because the current *Form 33* will capture any missed outcomes. Investigation and adjudication of outcomes is conducted during the close-out period and continues until the August 15, 2005 WHILMA database closure. Outcome priorities remain unchanged during the close-out period, therefore, prioritize CT over OS outcomes with the ultimate goal of having all outcome cases adjudicated and data entered on or before the August 15, 2005 database freeze.

16.13.6 Data Management

All WHI study forms must be entered into WHILMA no later than August 15, 2005.

16.13.7 Records Retention

WHI requirements indicate data and forms on participants who have signed an Initial Consent must be kept after the study has ended. *Form 2/3s – Eligibility Screen* on participants who did not sign an Initial Consent may only be discarded after they have been data entered. *Form 2/3s* on participants who have signed an Initial Consent may not be discarded. CCs are not required to keep records onsite.

16.13.8 Equipment

Participant visits for the Clinical Trial and Observational Study of the Women's Health Initiative are scheduled to end March 31, 2005. At that time, WHI clinical centers will no longer require certain items of equipment, such as scales, ECG machines, optical scanners, centrifuges, freezers, freezer alarm systems, cameras, furniture, refrigerators, microwave ovens, PCs, etc.

Some of the equipment was purchased by your institution and some was provided by the Clinical Coordinating Center (CCC) at Fred Hutchinson Cancer Research Center (FHCRC). Refer to Equipment Letter deated September 9, 2003 in Public Folders/Close-out folder for how to dispose of equipment.

16.14 WHI Extension Study and Supplemental Use Consents

16.14.1 Obtaining Consents for CT and OS Participants

Obtaining a participant's signed consent for enrollment in the WHI Extension Study and for the Supplemental Consent may be done by mail or in-person, as per local IRB requirements. CCs will mail the Extension Consent and the Supplemental Consent Forms to participants, either in the CT close-out visit packet or a separate OS mailing. CT participants who will not receive a close-out visit packet (i.e., participants with a follow-up status of no visit, proxy follow-up, etc.), may be sent an OS consent mailing packet. Ensure the correct Extension Study consent is used (i.e., HT consent for HT participants, and non-HT consent for all other participants). Refer to *Table 16.8 – OS Consent Packet Materials* for items to include in the mailings. Make sure that participant barcode labels are affixed to any consent forms that are mailed out. If the consent is collected by mail, refer to *Vol. 2, Section 16.14.4 – Collecting the Consents by Mail.*

Ideally, consents should be obtained after the close-out tasks are collected from both CT and OS participants. Each CC is responsible for obtaining consent for its own participants. The two consent forms are presented to all participants, with the exception of those with an "absolutely no contact" or deceased follow-up status. To obtain consent from participants on "proxy" follow-up, see *Vol. 2,Section 16.14.5 – Obtaining Consent Forms from CT or OS Participants on Proxy Follow-up*. Participants may choose to participate in the extension study and choose not to sign the supplemental consent. It is also acceptable for the participant to sign the supplemental consent and not participate in the extension study.

It is up to each CC to decide which staff members are in the best position to participate in the informed consent process. There is no training certification required of staff who will be consenting participants. However, it is expected that any staff involved in providing the consents will be fully knowledgeable of the consents' content, as well as the consenting requirements at their institution.

Extension Study Consent

In the spring of 2004 the National Heart, Lung, and Blood Institute approved a five-year extension study of all WHI participants to collect health information through 2010. The WHI Extension Study will help investigators learn more about long-term changes in women's health. All women who participated in WHI will be invited to join the Extension Study.

Two different informed consent forms have been developed for the Extension Study, depending on which component of the WHI the participant was in.

- The Extension Study (Non-HT) Consent is for women who participated in any WHI component other than the Hormone Trial (including OS).
- The Extension Study (HT) Consent is for women in the Hormone Trial, even if they also participated in other components of WHI.

Supplemental Consent (for use of stored specimens by non-WHI researchers at private or non-profit organizations)

When WHI began, participants consented to provide samples of their blood for future research by WHI investigators. These on-going studies have included genetics research to learn how differences in blood, blood proteins, and DNA might be associated with disease risk or health outcomes. The use of participants' blood samples for these studies by WHI investigators can continue under the existing WHI consent. However, we are now asking participants to sign a new, "Supplemental" consent so that WHI stored specimens can be made available to non-WHI researchers at private or non-profit organizations.

Since participants consented to join WHI, huge technological advances have been made in the ways scientists can analyze blood, proteins in the blood, and DNA. Scientists in settings outside of WHI and even outside of traditional academic and medical settings have been involved in making these scientific advances. In some cases, scientists at private and for-profit organizations and companies have the best

access to the experience and state-of-the-art technology needed to conduct these newer types of studies. The WHI would like to collaborate with these scientists so that further advances in science can be made and important public health questions can be answered. This collaboration is consistent with our promise to participants that we are using their health information and specimens to answer many important questions about women's health.

The Supplemental Consent, which discusses the sharing of WHI participant blood samples with scientists at for-profit and non-profit organizations outside of the WHI, must be obtained before the samples can be shared. All participants should be approached to sign the Supplemental Consent Form (*Vol. 2, Appendix E, Figure E.7.7)* regardless of which study arm they participated in.

16.14.2 Extension Study Consent Collected in the CC

16.14.2.1 Extension Study Talking Points

Background:

The National Heart, Lung, and Blood Institute has approved a five-year extension study of all WHI participants so that important health information can be collected through 2010. The WHI Extension Study will help investigators learn more about long-term changes in women's health. Women in the WHI Hormone Trials (even if they participated in other WHI CT components) will be asked to sign a "WHI Hormone Program Extension Study Consent." All other participants (including OS women) will be asked to sign the "WHI Extension Study Consent."

These talking points are intended for staff who will be discussing the WHI Extension Study with participants for the purpose of obtaining informed consent. This document can also serve as a resource for other WHI staff who may be asked about the Extension Study. Staff should read both the WHI Extension Study Consent and the WHI HT Extension Study Consent in addition to this document. More detailed procedures on carrying out the informed consent process with WHI participants (including HIPAA considerations) can be found in the "WHI Close-out Procedures" document and from your local IRB.

Key Points

Regardless of whether your clinic chooses an individual or group format to properly inform and educate women about the Extension Study, the following points should be covered :

- The purpose of the WHI Extension Study is to continue to learn about the health of postmenopausal women for an additional 5 years. Thousands of WHI participants are expected to participate in this study.
- You will **not** be asked to come into the WHI clinical center for visits. Each year you will be sent an annual health update (Medical History Update for all participants; an additional Hormone Questionnaire for HT participants) to complete and send back through the mail.
- FOR HT PARTICIPANTS ONLY: You will also be asked to have a mammogram each year for the first two years and to give us permission to obtain copies of the mammogram report.
- You might be asked to sign a medical release form to get more detailed information about health changes you have experienced.
- Any information you provide will be kept confidential. Only WHI staff will have access to this information. For safety reasons, Food and Drug Administration staff may also examine these records.
- No identifying information will be included in study reports; your health information will be grouped with information from other participants.
- There is no promise or guarantee that you will receive any personal benefit from the study. You should contact your own health care provider about any personal health issues or questions you may have.
- There are no risks to completing the health update forms.
- The study is completely voluntary and you may withdraw at any time.

Additional Points

The following additional points are appropriate to incorporate into your discussions with participants about why the WHI Extension Study is important.

For HT Participants:

- Women, health care providers, and scientists throughout the world are asking how women's risk for certain diseases change after they stop hormones. We need long-term data from WHI Hormone Program participants like you--women from the Estrogen-Plus-Progestin and the Estrogen-Alone studies and those who were the active and placebo groups of both studies--to get answers to these questions.
- Many women and their health care providers are evaluating and re-evaluating their hormone choices since they heard about the WHI Hormone Program findings. Just as you contributed to those important findings, your future choices about hormones--what types of medications, if any, you take--can help us learn more about the health effects of these choices.
- We have tried to make participation in the Extension Study as easy as possible—you will not need to come in for clinic visits or exams. The data for this study will come from forms that we send in the mail.
- To ensure your safety and learn more about breast health after women stop hormones, we will ask your permission to obtain your mammogram reports during the first two years of the study. We may also check in with you by phone to get information about where these mammogram reports or other health records are located. However, you do not need to come in to the clinical center anymore.

For DM Participants:

- The health effects of your past dietary choices may continue for years after the WHI Dietary Study has ended. This is true whether you were in the Comparison group and may not have changed the way you eat, or you were in the Dietary Change group and were asked to eat less fat and more fruits, vegetables, and grains.
- We invite you to continue with the WHI by joining the WHI Extension Study so we can answer questions about these longer term effects of diet.
- Your participation in this new phase of the WHI will help advance knowledge about the effect of diet on health in women.
- We recognize that the choice is yours and invite your questions.

For CaD Participants:

- The WHI Extension Study will allow us to answer additional important questions about the health effects of taking calcium and vitamin D. For example:
    - How long do women need to take calcium and vitamin D to prevent diseases like colon cancer and osteoporosis?
    - Does calcium and vitamin D prevent breast cancer?
    - If there are benefits or risks to taking calcium and vitamin D, how long do they last after women stop taking these supplements?

16.14.2.2 Review of Extension Study Consent

After reviewing the talking points, have the participant read (if she did not receive it ahead of time) or review the Extension Study (Non-HT) Consent or the Extension Study (HT) Consent. Following the reading of the consent form, allow ample time to answer any questions she may have. Refer to the "Extension Study FAQ" (Public Folders) to help answer her questions. If questions come up that are not in the FAQ, refer the participant to the appropriate staff (i.e., CP or PI) for further clarification.

If the consent process is being done in a group setting, smaller groups are advised to stimulate discussion. It is also recommended that women have the opportunity to ask their questions privately.

If the participant needs more time to consider if she wants to sign the consent, provide her with a postage-paid return envelope to return the consent at a later time.

16.14.2.3 Signing of the Extension Study Consent

Ask the participant to sign and date two copies of the consent form in the appropriate places. Sign and date one or two copies of the form as a WHI representative and witness, as required by your CC's IRB. Ensure participant barcode labels are on each copy of the consent form. Give one copy of the consent form to the participant to take home with her and keep one copy for her clinic file.

After the participant signs the form, thank her for her time. Let her know that she will be receiving a WHI newsletter in the mail about once a year. Remind her that she will start receiving her annual data collection packet within a year. Provide her with a number to call or postage-paid postcard to use for notification of a change of address.

After the participant signs the consent form (or declines), thank her for her years of dedication to WHI. Then initiate discussion of the Supplemental consent (see *Vol. 2, Section 16.14.3 – Supplemental Consent*).

Complete and data enter *Form 111 – Extension (Non-HT) Consent Status*, or *Form 112 – Extension (HT) Consent Status*.

16.14.3 Supplemental Consent (for use of stored specimens) Collected in the CC

16.14.3.1 Supplemental Consent Talking Points

Background:

When WHI began, participants consented to provide samples of their blood for future research by WHI investigators. These on-going studies have included genetics research to learn how differences in blood, blood proteins, and DNA might be associated with disease risk or health outcomes. The use of participants' blood samples for these studies by WHI investigators can continue under the existing consent. However, we are now asking participants to sign a new, "Supplemental" consent so that WHI stored specimens can be made available to non-WHI scientists.

Since participants consented to join WHI, huge technological advances have been made in the ways scientists can analyze blood, proteins in the blood, and DNA. Scientists in settings outside of WHI and even outside of traditional academic and medical settings have been involved in making these scientific advances. In some cases, scientists at private and for-profit organizations and companies have the best access to the experience and state-of-the-art technology needed to conduct these newer types of studies. The WHI would like to collaborate with these scientists so that further advances in science can be made and important public health questions can be answered. This collaboration is consistent with our promise to participants that we are using their health information and specimens to answer many important questions about women's health.

It is well understood that the field of DNA and genetic research is growing quickly and can be very complicated to understand. Even those who have significant health and/or science backgrounds can find themselves perplexed at times when answering specific questions related to DNA and genetics. It is recommended that staff review the basics so that they can feel as comfortable with the material as possible. A useful website to serve as a resource to staff is www.nlm.nih.gov/medlineplus/cloning/html.

An in-person discussion about the Supplemental Consent can be done individually or in groups, depending on the CC's specific needs and resources. These talking points are intended for staff who will be having discussions with participants for the purpose of obtaining informed consent. The talking points can also serve as a resource for other WHI staff who may be asked about the Supplemental Consent, how their samples are used, or genetics research in WHI. An optional participant video, introducing the concept of sharing WHI blood and DNA samples with outside scientists, has also been developed for CC use. It is recommended that women view the video to help them better understand the Supplemental Consent form and to generate some

enthusiasm for this opportunity to advance our knowledge of this growing field. The video will help answer potential questions and may cut down on staff time. The video may be shown individually or in a group setting.

In addition to these talking points, staff should read the Supplemental Consent and refer to the Supplemental Consent FAQ for suggested responses to participant questions that may come up. More detailed procedures and guidelines on carrying out the informed consent process with WHI participants (including any HIPAA considerations) can be found in the "WHI Close-out Procedures" document and from your local IRB.

Regardless of whether an individual or group format is used to inform and educate women about the Supplemental Consent, the following points must be covered (see "Supplemental Consent Talking Points" (Public Folders) for more details):

Key Points to Cover in Discussions with Participants about the Supplemental Consent:

- The use of blood samples by WHI scientists can continue under the original existing consent. This new "Supplemental Consent" is specifically asking for permission to share blood and DNA samples with non-WHI scientists at private or non-profit organizations, starting in 2006.
- Collaboration with these non-WHI scientists may lead to even more ways of analyzing samples and to faster development of new tests to diagnose and/or predict diseases.
- The National Heart, Lung, and Blood Institute (NHLBI) and our Institutional Review Board (IRB) will carefully review all research proposed by scientists from outside organizations according to high standards and ethical principles. No samples will be made available until these proposals are approved.
- Only those blood and DNA samples that have already been collected and are already stored will be made available to these non-WHI scientists. No additional blood or DNA will be needed, and you will not be asked to give more blood samples.
- All individual data in the WHI is kept confidential. No results of blood or DNA (genetic) studies done using your samples will be provided to you, or your family, doctor, or insurance company.
- The results of this type of research are reported on and applied to groups as a whole. We will not know what the DNA research shows for an individual person's health.
- Consenting to this supplemental use of blood does not mean that you are consenting to or will have genetic testing. You must speak with your own health provider if you are interested in having genetic testing.
- There will be no direct benefit from these studies to your own personal health, but this research will hopefully result in new tests and treatments to prevent or cure diseases.
- At any time, you may withdraw consent for any use of your blood or just for this supplemental use, without affecting your participation in other parts of the WHI.
- There are no costs to you or your insurance for any blood or DNA research using your WHI samples.
- Your blood and DNA samples will be stored at a central site listed under a code number only. No personal identifying information will be included on your samples.
- WHI has been granted a Certificate of Confidentiality from the US Federal Government to make sure that your confidentiality is protected.

16.14.3.2 Review of Supplemental Consent

Following the video, have the participant read the Supplemental Consent (*Vol. 2, Appendix E, Figure E.7.7*) (or review it, if she received it ahead of time). Following the reading of the Supplemental Consent form, allow ample time to answer any questions she may have. Refer to the "Supplemental Consent FAQ" (Public folder) to help answer her questions. If questions come up that are not in the FAQ, refer the participant to the PI for further clarification.

If the consent process is being done in a group setting, smaller groups are advised, to stimulate discussion. It is also recommended that women have the opportunity to ask their questions privately, if possible.

If the participant needs more time to consider the consent, provide her with a postage-paid envelope to return the consent at a later time. Make sure that the consent form copies that she takes with her have participant barcode labels affixed to them.

The field of DNA and genetic research is growing quickly and can be very complicated to understand. Even those who have significant health and/or science backgrounds can find themselves perplexed at times when answering specific questions related to DNA and genetics. It is recommended that staff review the basics so that they can feel as comfortable with the material as possible. A useful website to serve as a resource to staff is www.nlm.nih.gov/medlineplus/cloning/html.

As fields emerge and grow and technology advances, new situations and questions can arise. Not every question will have a clear answer at this point, since we don't know exactly how the field will evolve. It is important to understand that all WHI researchers and future collaborators will make every reasonable effort to uphold the toughest ethical standards for research with human subjects, including blood and DNA research.

16.14.3.3 Signing of the Supplemental Consent

Ask the participant to sign and date two copies of the consent form in the appropriate places. Sign and date one or two copies of the form as a WHI representative and witness as required by your CC's IRB. Place a participant barcode label on each copy of the consent form. Give one copy of the consent form to the participant to take home with her and keep one copy for her participant file.

If the participant declines to sign the form, thank her for her time.

Complete and data enter *Form 113 – Supplemental Consent Status* indicating the consent status.

16.14.4 Collecting the Consents by Mail

Use *WHIP0870 – OS Extension Consent Batches Screen* and *WHIP0148 – Follow-up Visit Information* to identify OS and CT participants, respectively, who are due for consenting. *WHIP9762 – Close-out and Extension Consent Tracking* can be used for tracking both CT and OS participants who have not completed the consents. See WHILMA upgrade notes Ver. 5.5 for detailed instructions on using WHILMA to identify OS participants and for tracking consents.

Once participants are identified as needing a consent mailing, mail the first consent packet, (see *Table 16.8 – OS Consent Packet Materials* for mailing packet contents). A second packet, identical to the first, can be re-sent to non-responders 2 months after the first two. CCs have the option of sending a third mailing, two months after the second mailing to non-responders. If there is still no response, the CC may try to contact these participants by telephone to discuss the possibility of then signing one or both consents. The amount of effort that goes into locating and obtaining consents from non-responders is at the CC's discretion.

Complete and data enter *Form 111 – Extension (Non-HT) Consent Status* and *Form 113 – Supplemental Consent Status* for all participants indicating the consent status.

16.14.5 Obtaining Consent Forms from CT or OS Participants on Proxy Follow-up

To obtain consent from CT or OS participants on "proxy" follow-up, start first with a contact with the designated proxy. Confirm with the proxy that the participant is competent to consider and sign the Supplemental Consent Form. Discuss also her ability to consider and sign the Extension Study Consent Form, and confirm with the proxy that he/she would be willing to continue completing annual health forms for the participant. If the proxy agrees that you can proceed with one or both consents, contact the participant and initiate the consent process.

Note that a proxy cannot sign either the Supplemental Consent Form or the WHI Extension Consent Form, unless he or she is the participant's power of attorney. Your local IRB may provide additional guidance on obtaining consent from participants on "proxy" follow-up.

16.14.6 Signing of the *Form 114 – WHI Genetic Studies Consent Status*

The *Form 114 – WHI Genetic Studies Consent Status* is completed only when a participant requests one of the following changes in her WHI genetic studies consent status.

- The participant requests that her blood not be used for WHI genetic studies; or
- The participant who previously asked that her blood not be used for WHI genetic studies on *Form 11 – Consent Status* now agrees to allow her blood to be used in WHI genetic studies.

This is not a routine task and the participant should not be prompted or asked about her previous WHI genetic studies consent status.

Table 16.8 – OS Consent Packet Materials

	OS Documents		Purpose	Source Location	Title in Public Folders	Manual
1	Cover letter for mailed consent packet (required)	All	A cover letter that introduces the Extension Study and Supplemental Use consents and Summary Worksheet	CC Prints Close-out/Packets/OS Consent mailing packet	Cover letter – OS Mail Consent Packet.doc	*Vol. 2 App. E.7.10*
2	WHI Consent Summary Worksheet (required)	All	Participant records her intention to either sign or decline signing of the Extension Study and Supplemental Use consents	CC Prints Close-out/Packets/OS Consent mailing packet	Consent Summary Worksheet.doc	*Vol. 2 App. E.7.11*
3	Cover letter - Extension Study Consent (non-HT) (required)	All	A cover letter to attach to the Extension Study consent mailed to OS participants	CC Prints Close-out/Packets/OS Consent mailing packet	Cover letter – OS Mail Extension Study Consent.doc	*Vol. 2 App. E.7.2*
4	Extension Study Consent (non-HT) (required)	All	Used to obtain informed consent for Extension Study (place a participant barcode label on both copies)	CC Prints Close-out/Packets/OS Consent mailing packet	Extension Study Consent (non HT).doc	*Vol. 2 App. E.7.3*
5	Cover letter – Supplemental Consent (required)	All	A cover letter to attach to the Supplemental Use consent mailed to OS participants	CC Prints Close-out/Packets/OS Consent mailing packet	Cover letter – OS Mail Supplemental Consent.doc	*Vol. 2 App. E.7.6*
6	Supplemental Consent	All	Used to obtain informed consent for the Supplemental Consent (place a participant barcode label on both copies)	CC Prints Close-out/Packets/OS Consent mailing packet	Supplemental Consent.doc	*Vol. 2 App. E.7.7*
7	Business reply return envelope with CC address (required)	All	For participant to return her signed consent forms to the CC	CC prepares	-	-

16.15 Post Close-out DM-C Newsletter (for DM-C only)

The purpose of the DM-C newsletter is to honor the WHI protocol commitment to provide an overview of the DM Intervention to DM Comparison participants at the time the WHI Dietary Study results become publicly available.

The newsletter will be written in light of the WHI results, hence is not yet completed. The four page newsletter will provide a snapshot of the DM Intervention: the dietary goals; design of the group sessions; and a summary of session content. It will offer a few choice-based behavior-change tips, such as self-monitoring and paying attention to serving sizes. The newsletter will provide a recommendation to see ones personal health care providers (including a registered dietitian) for dietary advice and offers guidance about where to find more information about nutrition, if a participant is interested.

The DM-C newsletter is designed for DM Comparison participants only. The CCC will mail the newsletter and a WHI Dietary Study update to all DM Comparison participants after October 1, 2005.

SECTION 16

FOLLOW-UP CONTACTS

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SECTION 17

RETENTION

INTRODUCTION

Retention in the Clinical Trial (CT) and Observational Study (OS) components of the Women's Health Initiative (WHI) is crucial to the success of the WHI. Retention refers to the overall strategies and procedures used to assure a participant's adherence, performance, participation, and contact in the study. Retention of study participants as defined by the study protocol is the dominant focus after the participant is randomized (CT) or enrolled (OS).

This section describes study-wide and local retention activities designed to keep participants interested and active in the study. These activities include enhancing participant identity with WHI, providing incentives for ongoing participation, and having regular, ongoing contact with study participants. Follow-up contacts conducted in a personal and motivating way allow the Clinical Centers (CCs) to continue a professional, caring relationship with the participant throughout the entire study, which will help maintain the participant's retention.

Every effort should be made to encourage full participation until the end of the study. Before a participant decides to discontinue participation in the study, specific retention activities should be conducted to encourage her to continue. Suggestions for dealing with those who are reluctant to continue as full participants in the study ("retention challenges") and strategies to promote adherence to study requirements are included in this section. In addition, procedures for locating hard-to-find or "lost" participants and transfer procedures for participants who move during the study are included.

Occasionally a participant will become unable or unwilling to fully participate in the study, necessitating a change in her participation status. Participation expectations for each component of the study and procedures for changing participation status, if necessary, are described in this section.

Participation status includes both intervention and follow-up status. A participant changes intervention status if she is not willing to participate in the WHI intervention(s) to which she was randomized or she needs to stop intervention for safety or other reasons. If full participation is not possible, it is important to maintain some form of contact with the participant. For example, a woman who insists on "dropping out" of the intervention should be encouraged to still come in for CC visits. For a woman who refuses CC visits, it is important to at least get agreement to contact her by mail and/or phone to follow her medical history. A participant's follow-up status changes if she is not willing or able to participate in full follow-up, if she cannot be located, or if she has died.

17.1 General Activities to Promote Retention

Retention of study participants is the primary focus of activity following enrollment or randomization in the WHI. Retention has several components: adherence (taking study pills), performance (maintaining low-fat dietary consumption), and participation (attending or completing DM Intervention sessions, attending follow-up visits, and accepting phone calls). Strategies and procedures to assure a participant's retention, adherence, performance, participation, and identification with WHI must be used throughout the course of the study, from initial screening to the last follow-up contact. Below is a list of retention enhancement methods; some are implemented on a study-wide basis (e.g., the newsletter), and some are recommended strategies for CC use (e.g., appointment reminders). Each CC should implement its own local retention efforts to complement study-wide activities and designate staff members with specific retention responsibilities.

A table at the end of this section (*Table 17.1 - Summary of Retention Activities*) summarizes retention activities for the various components of WHI and provides a quick reference to other Volume 2 sections dealing with retention and adherence issues.

17.1.1 Clinical Center Facilities and Operations

17.1.1.1 CC Environment

The CC environment should be clean, pleasant, and oriented to the comfort of the participant. A quiet waiting room area, an efficient reception and appointment scheduling area, appropriate reading materials and posters, and a clean, organized interview area are important. Pleasant experiences with the CC staff, visit contents, appointment scheduling, and exiting can all encourage the participant to continue in the study. A feedback mechanism for the participants, for example a suggestion box in the waiting area, may be a good idea.

17.1.1.2 Convenience and Accessibility

Aspects of convenience and accessibility include:

- telephone access
- CC location
- availability of transportation
- convenient clinic hours

Depending on local circumstances, different approaches may be used. Appointments should be available at times and on days that do not interfere with the participant's working schedule. All CCs should have at least some appointments available on evenings or weekends, outside of usual working hours. Pre-arranged parking should be available if at all possible. Maps, parking information, and public transportation information should be made available to participants.

Convenience and accessibility should be reviewed at each CC twice a year and obstacles eliminated to the greatest possible degree. Parking fee reimbursements or other travel expenses or arrangements may need to be considered by the CC if retention lags due to transportation problems. You may need to come up with creative solutions to help transportation problems. For example, local churches or other volunteer organizations may be able to help through the use of their van or other vehicles and/or by providing volunteers to drive participants to and from visits.

17.1.1.3 Time in Clinical Center

The length of a CC visit, as well as the time waiting for the visit, may be of vital importance in keeping participants returning for visits over a prolonged period of time. Try to keep total CC visit time on all visits to a minimum, but not be so brief at follow-ups that the travel time and effort seem excessive. It is especially important to keep waiting times to a minimum. If an extended waiting period becomes necessary, do what you can to avoid anxiety and hostility in the participant:

- encourage completing or review of study forms
- explain the situation and give the participant some alternatives from which to choose
- offer the option of seeing another staff member, if possible, or rescheduling if necessary
- have the daily newspaper, magazines, or other reading materials available.

17.1.2 Clinical Center Staff

17.1.2.1 Participant-Staff Relationships

A key element in successfully maintaining long-term participation is the development of a personal relationship between the individual participant and individual members of the staff. Good communication is essential to promoting and maintaining retention in the study. Consistency among staff and clarity of instructions are key to good communication. At all times, the participant should be helped to understand the beneficial nature of participation in the study. Encourage her to ask questions at visits, or to call between visits to clarify questions and problems that may arise. Assure participants that they should not hesitate to bring up any issues of concern.

17.1.2.2 Retention Specialist

It is recommended that each CC identify CC staff to serve as retention specialists. This staff member or members will participate in developing local retention strategies, will serve as contacts for Clinical Coordinating Center (CCC) retention activities, and will coordinate management of retention problems at the CC. Retention specialists should identify CC activities to promote retention that can be offered to women in each component of WHI.

17.1.3 Participant Identification with WHI (Required)

All CC staff should focus on promoting participant identity with WHI. Regular communication from the CC will encourage such identity. Building participant identity with WHI should begin during the recruitment process and continue through the end of the study. The following are suggestions for activities to promote identity with WHI.

17.1.3.1 Routine Contacts

<u>During Recruitment</u>

Early identification with WHI may enhance a woman's interest in joining the study. Inclusion of the WHI logo and catch-phrase "Be Part of the Answer" on brochures, posters, and other recruitment materials help promote identity with WHI. In addition, identify barriers to attending screening visits and develop procedures and materials to help overcome barriers. For example, send women maps showing the location of the CC clinic and transportation/parking information. Elevators and rooms should be clearly signposted with welcoming messages and the WHI logo. Distribute CC contact information: from the first contact, it is important to let women know that they are always welcome to call the clinic with questions or concerns.

Other activities or materials may be used to promote identity during recruitment, such as reports or letters from a significant person outside the study (e.g., community spokesperson, congressperson, governor) pointing out the importance of WHI and the valuable contribution being made by each participant. Thank you cards sent to potential enrollees following their initial screening visit may also encourage further participation in the screening process. These cards should stress the importance of the study and your appreciation to the participant for her interest.

<u>During Enrollment</u>

During enrollment/randomization into WHI, the participant receives a baseline welcome packet (see *Section 4.4.11 - Baseline Welcome Packet*) and other materials designed to promote identity with the study, including:

- WHI logo kit folder (required for CT and OS) - ordered through the CCC using *Form 172 - Supplies Order*

- WHI magnet with the CC name and telephone number (required for CT and OS) - provided annually by the CCC during the recruitment phase

- Membership Identification Card (required for CT and OS) - ordered through the CCC using *Form 172 - Supplies Order* (see *Section 17.1.3.3 - Membership Identification Cards*)

- "Welcome to the [study component]" handouts (required for CT and OS) - ordered through the CCC using *Form 172 - Supplies Order*

- WHI Calcium Handout (recommended for OS, required for CT, except for DM Intervention women who receive a modified low-fat version during their DM sessions) - ordered through the CCC using *Form 172 - Supplies Order*

- Component-specific Chart Stickers (recommended for CT and OS) - ordered through the CCC using *Form 172 - Supplies Order*

- Exercise Brochure (required for CT) - ordered through the CCC using *Form 172 - Supplies Order*

- Other NIH approved health brochures (recommended for CT and OS, CC discretion) - see *Section 2.3.2.6 - Other Equipment and Supplies* and *Section 17.1.3.6 - Health Information and Education*

- Contact schedule or appointment reminders (recommended for CT)

- Component-specific information, such as USDA Dietary Guidelines (DM Comparison group participants only) and Hormone Replacement Therapy (HRT) Handbook (required for HRT participants) (see *Section 4.4.13 - Participant Hand-Outs*)

During Follow-up

During follow-up, maintaining identification with the study is particularly important for retention. Identification is promoted by regular contact with the CC and by distributing materials that keep the participant connected to the study. The goal is to have some type of contact with every participant at least every six months, whether by mail, telephone, or in person. These contacts help promote retention in study activities. Identification after enrollment is achieved through several activities:

- Annual follow-up visits and contacts with the CC (See *Section 16 - Follow-up Contacts*)

- Incentives (see *Section 17.1.6 - Retention Incentives (Required)*)

- Participant Newsletter (CT and OS) - see *Section 17.1.5 - Participant Newsletter (Required)*

- DM Newsletter (DM dietary change participants only) - see *Section 6.12.2 - Newsletter*

- Birthday, thank you, anniversary, bereavement, and holiday cards - CCs are encouraged to maintain contact with participants by sending greeting cards to mark special occasions in the participant's life. Birthday (a new card is designed annually), thank you, and multi-purpose, generic cards can be ordered through the CCC using *Form 172 - Supplies Order*. (Run the *Happy Birthday Report (WHIP 0788)* for a list of participants with a birthday during any specified month.) Purchasing/designing and distributing other types of greeting cards (anniversary, bereavement, or holiday) is at CC discretion.

17.1.3.2 Involvement of Family Members

Encourage the support and involvement of participants' family members throughout WHI using the following strategies:

- Invite husbands, partners, or significant others to attend the CC visits, especially the initial visits, as well as special events held during the course of the study. Both retention and adherence are more likely if family members are involved in the process.
- Encourage family members to learn about the study's purpose and general design, and inform them of the ongoing safety monitoring of participants.
- Encourage family members to notify the CC if the participant becomes ill or happens to be out of town when contact is to be made or a visit scheduled.

17.1.3.3 Membership Identification Cards

Participant membership identification cards are distributed to participants at the time of enrollment (OS) or randomization (CT). The purpose of these cards is to provide a quick identification of the participant's name and study ID, give the participant easy access to her CC's telephone number, enhance identification and bonding with WHI, and provide the participant with a card to show her health care provider, if appropriate.

These wallet-sized cards are printed with the WHI logo and CC name and phone number on one side. A label including the participant's name, participant ID, and ID barcode is placed on the backside of the card at time of enrollment. At the same time, mark the participant's study component(s) with a permanent ink marker. The label may need to be replaced periodically throughout the study, depending on wear. Membership cards are ordered through the CCC using *Form 172 - Supplies Order*.

17.1.3.4 Participant Representative

Clinical Centers are encouraged to establish a participant representative to meet periodically with the CC staff. Representatives can provide CC staff with the participant's perspective on the WHI experience. She may be able to help address barriers to retention by making suggestions, for example, about enhancing the waiting room environment, helping to deliver educational and informational materials, organizing alternative or cooperative transportation, and providing feedback from other participants.

17.1.3.5 CC Group Events and Activities

Clinical Centers are encouraged to plan events and activities to promote retention. The frequency of retention events and activities is at the discretion of the Clinical Centers. Clinical Centers are encouraged to consider their own CC's retention data and resources when considering the frequency of events and activities.

Open house events where all WHI participants are invited to attend are permitted, if study component information is not made apparent. During studywide events, care should be taken to avoid contamination between DM Dietary Change and Comparison groups. Topics for discussion at events and social activities should focus on information not related specifically to one study component or another and should not include discussion of topics relating to WHI interventions (e.g., nutrition) or outcomes. For example, it is okay to present health information such as tips for quitting smoking, but is not okay to present information on ways to prevent heart disease. Discussion of study progress (e.g., number of randomizations to date) is appropriate. Non-health related activities, for example, fashion shows or WHI birthday parties are allowed. During events, express appreciation for participating in the WHI and reinforce the importance of every participant's continued involvement to the success of the study.

Foods served at CC-wide events should include moderate- or high-fat choices as well as low-fat choices, similar to the acceptable cultural foods of your region. Although low-fat choices should not be stressed, avoid serving "junk" food or foods that send an unhealthy message; given that this a study on women's health, we don't want to promote the use of unhealthy foods. Fat content of foods should not be labeled and recipes should not be provided. If a separate meeting is held for Dietary Change participants, then it would be appropriate to serve only low-fat foods and to provide recipes. For DM participants, CCs should focus adherence and retention efforts on Dietary Change group participants rather than on DM Comparison group participants.

The following is an example of a studywide event: A "WHI birthday party" to celebrate the WHI is held. All participants (CT and OS) are invited, and they may bring a spouse or guest. Participants are asked in advance not to identify themselves by group assignment. A large hall is rented as the site for the reception, and a variety of low-fat and "regular-fat" foods are available. In addition, a large number of door prizes, donated by local merchants, are distributed. After a brief overview of WHI recruitment progress, an invited speaker presents a brief talk of interest to participants.

17.1.3.6 Health Information and Education

Both CCC and CC staff will address participant health information and concerns in standardized formats. Some suggestions for distribution of health information are the following:

- Create a distribution center or display for free health-related (not diet-related) materials in the waiting area or other convenient, accessible location. Free publications approved by the National Institute of Health (NIH) for WHI distribution (see *Section 2.3.2.6 - Other Equipment and Supplies*) can be ordered from the NIH by calling 1-800-4-CANCER. Publications not on this list need NIH approval before being distributed to participants. Health materials developed by the CC must be approved by the CCC, following the standard procedures for CC materials review, before distribution at the CC. The display might include copies of the informed consent forms for participants to read again, if interested, or health educational videos for viewing on site or at home.
- Compile a list of all local services and programs for health promotion (e.g., smoking cessation) and for special support groups (e.g., bereavement, cancer). Copy and display this list at the distribution center. Make these referral sheets available for participants at each local site.
- Invite participants to health promotion events that do not interfere with WHI interventions, such as sessions on smoking cessation or administering CPR.

17.1.4 Tracking (Required)

17.1.4.1 Tracking System for Study Visits

The Post-Randomization Visit Reminder (*WHIP 0787*) is a WHILMA report generated by CCs that lists, by target date, all women who are due for a given post-randomization follow-up visit during a specified time period. This report should be used with your CC's system to track and set up participant follow-up contacts.

17.1.4.2 CC Visit Appointment Reminders

During the screening and randomization phases, when the CC process is still relatively new to participants, CC staff may contact participants by telephone to remind them of upcoming CC appointments, check to see if they have questions or concerns, and make sure they are properly prepared (e.g., fasting, wearing light clothes).

During follow-up visits, use appointment reminders to prompt participants to come for CC visits and to bring their current medications, study pill bottles, forms, and food records with them. These reminders can be postcards, telephone calls, or letters. To save time, you may want to send a postcard or letter to the participant well before the visit time window, reminding her that she is due for a visit and asking her to call the clinic for an appointment.

During all contacts, use procedures to aid participants in overcoming any reluctance to attend follow-up visits, such as a discussion of transportation reimbursement or daycare facilities, if available. Remind participants at each follow-up visit that they have ready access to study personnel. Specify the days and hours for your CC, as well as after-hour contacts. Encourage participants to call with questions, concerns, or symptoms.

17.1.4.3 Thank You Cards Following CC Visits

You may want to send a thank you card or postcard following attendance at clinic visits, either screening and/or follow-up visits. Stress the importance of these visits and your appreciation to the participant for taking the time to come into the clinic. Thank you cards can be ordered through the CCC using *Form 172 – Supplies Order.*

17.1.4.4 Maintaining Up-to-Date Personal Information on Participants

It is important to maintain contact with participants for the full duration of the study to ensure that study results are valid and, at the very least, to ensure that vital status (dead or alive) is known on each participant at the end of the study. The task of maintaining contact with participants will be facilitated by maintaining up-to-date personal information in each participant's file. Although participants are not required to answer every question on *Form 20 - Personal Information*, encourage them at a minimum to complete questions on full name including middle initial; address; phone number; the names, addresses and phone numbers of two personal contacts; Social Security Number; and name of health care provider. It is generally preferable to have personal contacts who are younger than the participant, in good general health, and who are not likely to move during the course of the study.

It is important to confirm during follow-up contacts that information on the participant's name, address, phone number, personal contact information, and health care provider is still current. This information should be reviewed at least once a year with the participant, even if she does not visit the clinic. If any of this information has changed, the participant should update *Form 20 - Personal Information,* and the participant's personal information should be updated on the member screen in WHILMA. This will minimize the possibility of participants becoming "lost" at any subsequent stage of the study. Participants should be asked to provide the name of a new personal contact if either of the personal contacts named at the start of the study is no longer suitable to act as a contact person.

17.1.4.5 Maintaining Complete and Deliverable Participant Addresses

When a participant's address is found to be no longer valid, the undeliverable address should be flagged on the participant's member screen and activities should be initiated to establish the participant's new address (see *Section 17.2 - Locating "Hard to Find" Participants*). Each month, CCs should run two reports to help maintain up-to-date and deliverable addresses in WHILMA (see *Vol. 5- Data System, Section 9.2 - Reports* and *Appendix D - WHILMA Reports* for information on running these reports):

- *WHIP 0611 - Members With an Incomplete Address or Long Name/Address*. This report provides a list of all (CT and OS) participants with a problem address (e.g., the address is incomplete or will not fit on a mailing label). Participants with address lines that are too long should be fixed immediately by using address line 2 for the second line of the address, or abbreviating words in the first line so that it stays within the 30 character width limit of the mailing labels. Those that are incomplete should be investigated as soon as possible. If the zip code is missing, try calling the post office or, if that fails, call the participant to obtain the correct address. If you cannot fix the address right away, set the undeliverable address flag on the "Contact Information Screen" in WHILMA. This will prevent mailings, such as OS follow-up mailings or the participant newsletter, from being sent to an undeliverable address. Try to fix incomplete addresses within two weeks of their appearance on the report. Participants will continue to appear on this report until either the address has been fixed or the "undeliverable address" flag has been set.

- *WHIP 1211 - Undeliverable Address Report.* This report provides a list of all (CT and OS) participants with undeliverable addresses (indicated by the undeliverable address flag) in the CC's database. The report does not include those with participation status of "no follow-up", "deceased", or "lost to follow-up". Items that may appear on the report are the participant's name and (undeliverable) address; participant ID; home phone; work phone; a note indicating that the workplace should not be contacted, if applicable; best time to call; phone of other contact; follow-up status; and date the undeliverable address flag was turned on.

  For participants appearing on this report, attempt to correct the address by contacting the participant at home and, if necessary, at work. If these attempts fail, telephone her personal contacts using information listed on the

report. If preliminary attempts to contact the participant fail, initiate a formal search to locate the participant (see *Section 17.3.1 - Initiating a Search to Locate Participant (Form 23) (Required).*

Undeliverable addresses should be updated as soon as possible, since a participant will not receive any mailings until the address is fixed. The sooner you try to get an address correction, the more likely you will be successful in tracking down the participant. Undeliverable addresses should be corrected within one month of appearing on the report. Participants will continue to appear on this report until the "undeliverable address" flag has been removed or follow-up status changes.

17.1.5 Participant Newsletter (Required)

All CT participants receive a trial-wide WHI newsletter (*WHI Matters*) twice a year during the fifth and tenth months after the anniversary of their enrollment month; OS participants receive the newsletter once a year during the fifth month after their enrollment anniversary month. The goal of the participant newsletter is to present news about WHI in an interesting and readable fashion, to encourage retention of study participants, and to promote participant identification with WHI as an important, national research effort. The newsletter is also useful in keeping up-to-date addresses for participants. All participants, unless otherwise requested, receive the newsletters at their home addresses. Clinical Centers are responsible for documenting on *Form 7 - Participation Status* those participants who request to be deleted from the newsletter mailing list.

A newsletter written specifically for DM dietary change participants is also distributed three to four times per year. For information about this newsletter, see *Section 6.12.2 - Newsletter.*

17.1.5.1 Production and Distribution

The CCC is responsible for the production and distribution of the annual newsletters, including content, design, layout, graphics, production costs, and coordination of printing through the Government Printing Office. Staff members at the CCC or any of the CCs are welcome to contribute ideas or articles for consideration. The CCC is responsible for keeping CCs informed of deadlines relating to submission of these articles.

The CCC is responsible for the mailing of the annual newsletters to CT and OS participants. Clinical Center-specific return addresses are printed on the newsletters mailed to that CC's participants.

17.1.5.2 Content

Newsletters include both project-specific and general, health-related information. Each newsletter includes the following general content areas:

- A column from the WHI Director at the NIH describing the progress and importance of the WHI.
- A section with articles on relevant health topics (not diet related).
- A section describing overall progress on study activities.
- A section with features and interviews of WHI participants.
- A section featuring segments submitted by and about the CCs (optional).

The following guidelines are to be followed for all newsletter submissions:

- Articles should be written at a 6th grade reading level; a slightly higher level may be acceptable for more complex articles, such as science or health articles.
- Original sources for articles, such as articles reporting the results of scientific research, will be carefully consulted for technical accuracy and kept on file at the CCC.
- When quoting an individual, the interviewer must ask the individual for permission to quote him or her. Quotes must be used verbatim, with quotation marks. Quotation marks are not used unless a direct quote is cited.

- If quotations are used from sources such as magazines, journal articles, or books, permission must be obtained from the publisher. This information is cited at the end of the article (for example: used with permission, name of source, date). When contacting a source to obtain permission, be sure to identify yourself as a non-profit research organization; permission will usually be granted without a fee. When reprinting cartoons, permission must be obtained from the syndicate that represents the cartoonist.

The newsletter staff and Project Directors at the CCC make initial discretionary decisions regarding newsletter content, appropriateness of articles, readability level, layout, and emphasis in coverage. Before final approval by the Project Office and Steering Committee, a draft of the newsletter is sent to the following committees for input and approval: Behavioral, CC Staff Group, Observational Study, and Special Populations.

17.1.5.3 Updating Addresses for Undeliverable Newsletters

One purpose of the participant newsletter is to help CCs make sure that they have up-to-date address information for each participant. A mailing label for each participant's newsletter is generated at the CCC based on the address listed on the Personal Information Screen in WHILMA. When the address on the mailing label is incorrect and the newsletter is not deliverable, the local Post Office will notify the CC. This notification is in the form of a photocopy of the mailing portion of the newsletter, along with address correction information (because newsletters are mailed bulk rate, undeliverable newsletters are neither returned nor forwarded to the new address). The CC is charged for each notification of an undeliverable address ($.50 per address as of 10/95). Update the contact information screen in WHILMA immediately when an address correction notification is received to ensure that future mailings are sent to the correct address and to avoid additional postal charges.

When a CC is notified of an updated address, the CC should try to contact the participant by telephone to make sure that her telephone number is still current. If this contact is made as soon as the CC is notified of the change of address, there may still be a recorded message with the new number, if it has changed. If a new telephone number is obtained, update the Personal Information Screen in WHILMA.

If a participant has a changed address, the Post Office does not forward the newsletter. The CCC will send an extra supply of newsletters annually to each CC. When you are notified of a new address, you may want to put one of the extra newsletters in an envelope and mail it to the participant at her new address; otherwise, she will not get a newsletter that year. Another option is to notify the CCC of the change, and a new newsletter will be sent to the participant from there. Note: you may not mail the newsletters using the "Bulk Rate" permit printed on the newsletters. This is for CCC use only and misuse by CCs can result in the cancellation of the CCC's mailing permit.

If address correction information is not available (i.e., "forwarding address unknown"), set the undeliverable address flag on the "Contact Information Screen" in WHILMA and initiate procedures to locate the participant. Try to contact the participant and, if necessary, telephone her personal contacts using information listed on *Form 20 - Personal Information* to get an updated address. If preliminary attempts to contact her fail, initiate a formal search to locate the participant [see *Section 17.3.1 - Initiating a Search to Locate Participant (Form 23) (Required)]*. Participants with an undeliverable address will appear on the *Undeliverable Address Report (WHIP 1200)* the next time it is produced (see *Section 17.1.4.5 - Maintaining Complete and Deliverable Participant Addresses*).

If the Post Office indicates that the participant is deceased, initiate contact with persons listed on *Form 20 - Personal Information*. If a death is confirmed, update *Form 7 - Participation Status*, complete *Form 120 - Initial Notification of Death*, and process according to procedures outlined in *Volume 8 - Outcomes.*

17.1.6 Retention Incentives (Required)

All participants coming in for annual visits receive a retention incentive provided by the CCC. In addition, Clinical Centers may provide their own incentives, within budgetary constraints, in the form of small gifts (e.g., pencil, lapel pin, t-shirt) or health information (non diet-related). Incentives will generally include the WHI logo to promote identification with the project.

17.1.6.1 Annual Incentives Provided by CCC

The CCC produces and delivers to the CCs one retention incentive (e.g., magnet, mug, bookmark, pocket planner) per year for each CT participant and guidelines for distribution at the annual visit. The CCC also provides a retention incentive for OS participant attending their Year 3 annual visit. Selection of annual incentives is subject to approval by the Behavioral, CC Staff Group, and Special Populations Committees.

17.1.6.2 CC Incentives

Each CC may use its own incentives for increasing participant retention. Examples of incentives are small gifts (e.g., t-shirts, bags, certificates of appreciation), educational materials (e.g., non diet-related health brochures), coupons (e.g., free coffee or soft drink from local cafe), or raffle tickets for small prizes (e.g., every participant who comes in for a follow-up visit is entered in a monthly drawing for a small prize). Clinical Centers may purchase incentives, if their budget allows, or obtain donated incentives from outside sources. If incentives are donated from outside sources, it is important that the WHI not appear to endorse a particular company or product. Therefore, a donated incentive cannot include both the WHI logo and the sponsors name or logo, unless a disclaimer of endorsement of the sponsor appears on the incentive.

17.1.6.3 Distributing Incentives

All participants should receive an annual retention incentive when they come in for their annual visit. It is probably easiest to hand out the incentive at the same time during each visit; use whatever timing works best for you. If a participant does not attend her annual visit, try to mail that year's incentive to her.

Research shows that incentives can help improve retention when their distribution is accompanied by a positive message. Please take the idea of an incentive seriously. When the incentive is distributed, be sure to stress that this is a token of our appreciation for her time and effort. For example, you may want to say something like:

"Thank you so much for your ongoing participation in WHI. As a token of our appreciation for your efforts, would you please accept this [incentive]? We know it is a small measure of the time and effort that you have put into the study so far, but we want you to know how important you are to us. Because of your contribution and the contributions of other women like you, we will be able to answer important questions about women's health. Remember, you are part of the answer! Thanks again, and we hope you enjoy the [incentive]!"

17.1.7 Media Relations and Handling Adverse Publicity

All sites would be well advised to pre-plan, as much as possible, their organizational response to media inquiries should a controversial announcement or event occur. Identifying spokespersons, establishing response protocols in advance, and communicating this information to all staff can help to minimize disruption. It may prove helpful to set up protocols and divide responsibilities for handling inquiries from the press, participants, and other key audiences should the need arise. In some cases, especially when a national or study-wide response is needed, the NIH Project Office is likely to supply talking points and a referral list of national WHI spokespersons to the CCs.

In all situations, crisis or otherwise, credibility is the key to successful media relations. With reporters, always be honest, brief, direct, and calm. Never say "no comment" and never "go off the record". Do not avoid or ignore a reporter's call. Honor deadlines. Be factual, accurate, and timely in your responses. Do not be argumentative or defensive. Cultivate positive and professional relationships with reporters and follow through appropriately. If facts or remarks end up not being accurately represented, contact the reporter immediately and politely request that the correct information be supplied to their audience. This may not always result in a retraction or a correction, but it will put the reporter on notice that you are vigilant, focused on accuracy, and willing to work with them to produce better quality stories for their audiences.

Whenever you are representing WHI on a national level, make sure that your comments apply to the study as a whole, and not to just your own CC. Information that is not accurate for the study nation-wide can generate a lot of work for other centers who may then have to spend time responding to participant inquiries and clearing up misconceptions resulting from the interview or story.

17.2 Clinical Center Activities for Retention Challenges (Required)

Clinical Centers are required to initiate special retention activities for those participants identified as "retention challenges". A participant is considered to be a "retention challenge" if she wants to change her participation status in the study, i.e., if she is no longer willing to fully participate in the intervention to which she was randomized or she is not willing to fully participate in follow-up activities.

There are two types of participation status:

1) Intervention status, the degree to which a CT participant is willing to participate in the WHI intervention(s) to which she was randomized. CT participants having problems with adherence to the intervention (e.g., an HRT participant who is unwilling to take her study pills) are considered intervention retention challenges and require special retention activities.

2) Follow-up status, the degree to which a CT or OS participant is willing to participate in follow-up activities. CT and OS participants who refuse follow-up visits and/or contacts are considered to be retention challenges, as are those who consistently miss visits without actually refusing to participate. Both types of follow-up retention challenges require special retention activities.

Before removing a participant from full intervention and/or full follow-up activities, CC staff should conduct special retention activities to try to reverse the participant's decision to reduce participation and maintain retention in all relevant aspects of the study (unless safety is an issue).

Those participants who decide to reduce their participation level can usually change one aspect of their participation and continue to maintain activity in the other aspects of WHI, i.e., even when a participant has dropped out of the intervention, the CC should still maintain her follow-up participation, unless otherwise requested.

Refer to *Table 17.2 – Summary of Clinical Center Activities for Retention Challenges* for an overview of procedures for retention challenges by study component.

Refer to *Section 17.4 - Changes in Participant Status* and *Form 7 – Participation Status*) for information about changing participation status.

17.2.1 Identifying Retention Challenges and Tracking Special Activities

Most participants will perform their WHI activities as planned with no retention difficulties. Some participants, however, will want to reduce or eliminate their intervention or follow-up participation status due to a variety of reasons. These retention challenges need more attention and motivation from CC staff.

Use the general model described below to try to identify participants who are retention challenges before they are lost to follow-up or decide to drop out of the study. Detailed information on conducting special activities specific to study component is located in the following sections: for HRT/CaD intervention challenges, refer to *Section 17.2.2.2 – Initiating Special Activities for HRT and CaD Retention Challenges*; for DM intervention challenges, refer to *Section 17.2.3.2 – Initiating Special Activities for DM Retention Challenges*; for CT and OS follow-up challenges, refer to *Section 17.2.4.2 – Initiating Special Activities for Follow-up Retention Challenges*.

- **Conduct Standard Procedures.** Ensure that all standard procedures as listed in *Sections 5 (HRT), 6 (DM), 7 (CaD), 8 (OS), 15 (Medications), 16 (Follow-up Contacts)*, as well as this section, have been attempted to maintain the participant's full participation in WHI.
- **Identify Retention Challenges.** Develop a system for identifying retention challenges (e.g., regularly review WHILMA reports on adherence, note women who miss annual appointments) and initiate special activities as soon as possible. Specific ways to identify intervention retention challenges for each part of the CT are listed in *Section 17.2.2.1 – Identifying HRT and CaD Intervention Retention Challenges* and *Section 17.2.3.1 – Identifying DM Intervention Retention Challenges*. Identify follow-up retention challenges is described in *Section 17.2.4.1 – Identifying Follow-up Retention Challenges*.

- **Conduct Special Retention Activities.** Attempt special retention activities as appropriate to promote retention. The CC should develop its own list of possible special retention activities that fit within the CC budget, preferences, and judgments. Try different activities for each participant, depending on previous experience with the participant and with her particular problems. Involve the appropriate intervention staff in making decisions about choice of activities. In addition to the special activities described below, refer to *Table 17.3 – Reasons for Poor Retention and/or Adherence* to help better understand some of the reasons participants may have with adhering and staying in the study, and *Tables 17.4 - Strategies to Retain Full Participation in CT and OS, 17.5 - Strategies for Adherence to CT Intervention,* and *17.6 – Examples of Retention Strategies.*

  It is at the CC's discretion to decide whether or not to complete retention activities in specific situations or for certain women. For example, when a participant reports that her doctor has told her to go off WHI HRT study pills so that she may go on (active) HRT, some CCs may conduct retention activities (attempt to discuss the importance of the WHI trial and alternative treatments with the woman and/or her physician), while other CCs may decide to not interfere in the doctor-patient relationship. Similarly, when a woman says she is too ill to continue on intervention, CCs should decide whether or not to conduct retention activities, depending on the type and severity of her illness and other factors.

  Participants who say they want to become inactive often change their minds after a "cooling off" period, so waiting for a few weeks or more may be appropriate. If a participant indicates that she wants no further contact with WHI, retention activities should be put on hold for a few months. After this period, CC staff may attempt to dissuade her from inactivation. Each CC should develop a system for tracking participants during this period.

- **Conduct Retention Meetings Regularly.** Staff with retention responsibilities should hold regular meetings to discuss general and participant-specific retention issues. These staff include but are not limited to the Clinic Manager, Lead or Group Nutritionist, Clinic Practitioners, the Principal Investigator or designee, Behavioral Scientist, and any other staff identified as retention specialists. Each CC should identify the key retention staff and schedule regular meetings to meet the needs of the clinic flow. Use these meetings to discuss general ideas for improving CC-wide retention, adherence, participation, and other interactions with participants. Discuss specific participants who pose retention challenges at these meetings and decide upon a course of action with the appropriate staff present. Before changing the status of any participant (see *Section 17.4 - Changes in Participant Status*), obtain agreement at a meeting that all strategies have been exhausted and that changing status is the only option open at this point.

- **Document and Track Special Activities.** When a contact has been made to conduct special retention activities with a participant who has a retention (or adherence) problem, complete and data enter a *Form 24 – Adherence and Retention Worksheet* to help document and track activities (refer to *Vol. 3 – Forms, Instructions for Form 24 – Adherence and Retention Worksheet* and *Vol. 5, Appendix B.3.4 – Adherence and Retention Worksheet)*. This optional worksheet can be helpful by keeping track of which participants have received contacts, recording the result of the contacts, and identifying participants needing further retention assistance. If additional retention contacts are needed following the initial contact, complete the "date for next contact" portion of *Form 24*. The names of participants needing additional contact, as indicated on *Form 24*, will then appear on the *Member Adherence and Retention Activity Tracking Report (WHIP 1238)* to help CCs keep track of the need for and timing of additional contacts.

  A new *Form 24* should be completed for each special retention activity. Note that *Form 24* is for special activities that occur between participants with retention problems and the CC primary contact for that activity (e.g., Lead or Group Nutritionist for DM Intervention, Clinic Practitioner for HRT and CaD, Interviewer for missed follow-up visits, etc.); *Form 24* does **not** need to be completed for routine retention activities (e.g., newsletters, appointment reminders).

  Although use of *Form 24* is optional, its use is strongly encouraged as a way to help track activities, especially by CCs who do not have other retention activity procedures and tracking systems in place. Note that there is not a "right" or "wrong" way to use *Form 24*. CCs should use the form in whatever way it is most useful in helping them track retention activities.

- **End Special Activities.** If special retention/adherence activities have not been successful and the participant insists on "no" or "less than full" participation in follow-up or "no" participation in intervention, refer to *Section 17.4 - Changes in Participation Status*.
- **Re-Contact Non-Participants Occasionally.** Contact participants with less than full participation status at least once a year throughout the study to see if they are willing to resume some or all aspects of their participation (see *Section 17.4.5 - Reactivation of Participants with Changes in Participation Status*).

17.2.2 Special Activities for HRT/CaD Intervention Retention Challenges

This section describes special activities designed for retention challenges enrolled in the HRT or CaD intervention study component. It includes information on identifying HRT and CaD Intervention retention challenges, initiating special activities for retention challenges, tracking and documenting special activities, and ending special activities.

17.2.2.1 Identifying HRT and CaD Intervention Retention Challenges

Intervention retention challenges in HRT and CaD are defined as having either low adherence (less than 80% of study pills) or non-adherence to the intervention's pill taking regimen. Participants identified as retention challenges require special retention activities to improve adherence (refer to *Section 17.2.2.2.1 – Intensive Adherence Program (IAP)* for specific procedures).

Clinical Center staff may identify HRT or CaD intervention retention challenges at a clinic visit, telephone contact, mail contact, or through discussion with other CC staff. Retention challenges in HRT and CaD can be identified in at least four ways:

- Participants with a calculated adherence rate of less than 80% at a clinic visit, based on pill weights or pill count estimates. However, if a participant has poor adherence but a concrete, reasonable reason for such poor adherence rate (e.g., loss of the pill bottle, inability to return to the CC to obtain more pills in time, illness), she may not require special retention activities.
- Participants with responses to the adherence questions on *Form 10 - HRT Management and Safety* or *Form 17 - CaD Management and Safety* that indicate adherence problems. Both *Form 10* and *Form 17* contain an item to check if the participant should be referred to the IAP based on the interview.
- Participants who CC staff determine need more assistance with adherence regardless of the adherence rate calculated. Examples of participants who may need special retention activities even though they meet the guidelines for good (>80%) adherence are:
  - Participants who the CC interviewer feels could benefit from a more systematic approach to adherence discussion. This could occur if the interviewer has limited discussion skills or minimal experience with adherence problems, or sees a situation with multiple or diverse adherence problems.
  - Participants who express concern about study pill symptoms or impact on health problems.
  - Participants who anticipate or are going through major changes in their routines, such as illness or death of a family member, extended trip away, etc.

While a participant is not removed from active HRT or CaD intervention status for low adherence, achieving an adherence of rate of at least 80% is desired if the goals of the study are to be met.

Refer to the *HRT/CaD Medication Adherence (WHIP 1260)* report to identify which HRT/CaD women need special retention activities to improve their adherence. Also refer to *17.2.2.1.3 - Documenting and Tracking Special Activities for HRT/CaD Retention Challenges* for a list of other reports and forms that may be useful in identifying which HRT/CaD participants need special activities.

17.2.2.2 Initiating Special Activities for HRT and CaD Retention Challenges (IAP)

When a participant has been identified as an HRT or CaD retention challenge, initiate the special retention activities outlined in *Section 17.2.2.2.1 – Intervention Adherence Program (IAP).* To help keep track of special activities, complete *Form 24 – Adherence and Retention Worksheet.*

Section 7.2.2.2 - Dealing with Non-Adherence, and *Tables 17.3 – Reasons for Poor Retention and/or Adherence, 17.4 - Strategies to Retain Full Participation in CT and OS, 17.5 - Strategies for Adherence to CT Intervention,* and *17.6 - Examples of Retention Strategies* provide interviewers and CPs with additional items for discussion and ideas for improving adherence and retention of HRT/CaD participants. These are methods of identifying participants who have poor adherence before they become non-adheres.

17.2.2.2.1 Intensive Adherence Program (IAP)

Adherence to study pills is an important part of the WHI study design and critical for testing the study hypothesis. The Intensive Adherence Program (IAP) is a series of special non-data-collected participant contacts aimed at improving poor adherence and dealing with pill adherence problems. IAP contacts are made with participants who report low adherence or because of CC staff referral for adherence problems. The number, frequency, and content of the contacts vary according to participant need and CC staff discretion.

IAP Staff

The CC staff person(s) initiating and coordinating the IAP (IAP Coordinator) must have experience and skills in communication, adherence monitoring, and study pill dispensation. Some C.c.s will have more than one IAP Coordinator and will assign a specific coordinator to a specific participant based on CC developed criteria. This coordinator may be a CP or directly monitored by the CP. This person should also be one of the primary contacts for the participant at the CC to increase rapport and promote consistency and continuity in participant contacts.

Initiating the IAP

Initiation of the IAP comes from the CC staff person(s) coordinating the program at your CC. The method of initiation is the same, regardless of how the participant was identified. Use the *IAP Checklist* to assure good communication and documentation of strategies used (see *Figure 17.2 - Intensive Adherence Program Checklist*). Complete the top portion of the *IAP Checklist* with the participant information and the reason for enrollment into the IAP. If the IAP Coordinator is available, the participant can be enrolled in the IAP immediately at the time of identification. If the IAP Coordinator is not available, the CC staff can let the participant know that someone will follow up with her on a future phone call. Use *17.3 - IAP Participant Call Record* to help track call attempts and contacts

Number of IAP Contacts

There should be at least two contacts made with the participant for the IAP: one to initiate the IAP and one to follow-up. The IAP Coordinator decides how many contacts are needed, balancing participant need with CC workload. The participant should also be encouraged to request more calls as needed.

Content of IAP Contacts

The content of the IAP contacts will vary, but include defining the specific nature of the adherence problem, self-monitoring of the problem, identifying solutions for the problem, and follow-up to see if the solutions worked in either eliminating the problem or making it better. The focus should be on the behavioral, symptom-related, cognitive, and affective reasons for poor adherence and what to do about them (see also *Table 17.3 - Reasons for Poor Retention and/or Adherence*).

IAP contacts should follow the simple steps described below. Suggested materials produced for use in the program to help guide the staff person through the steps of the program are included in this section.

1. Define the specific nature of the adherence problem.

   Discuss with the participant her adherence patterns during her time with WHI. Many adherence problems will have shown up before in similar ways. Discuss her adherence during the most recent period and the specific problems recently identified. Identify the point at which the participant started having difficulties, the time course (whether episodic or constantly occurring), and the participant's best guess as to the cause of the adherence problem. If the participant does not think she has an adherence problem per se, review her adherence in the very recent past. Ask for times that the participant has forgotten to take the pills and what those times were like.

   End this initial discussion with an "assignment" for the participant to self-monitor for a limited period of time to obtain more information about pill-taking behavior. Ask the participant to record in a diary her own monitoring of adherence (*Figure 17.4 - Daily Adherence Diary*). Negotiate the length of time and approximate dates of this self-monitoring. The minimum time for self-monitoring should be at least one week; longer would be better. Complete the information in the upper left hand corner of each diary page. Complete each cell of the Day/Date column on each diary page for each week. Send these pages to the participant and record the date and your action on the *IAP Checklist*.

2. Review the participant's self-monitoring activity.

   The purpose of reviewing the self-monitoring activity is to identify the cues and reinforcers for the adherence problem. Record pertinent information on the *IAP Checklist* as you discuss the following topics with the participant. Ask the participant to refer to her Diary during this discussion. Below are categories of cues and reinforcers that influence adherence. Point out specially any experiences or Diary notations that fall in these categories and discuss them in more detail with the participant.

   - Symptoms. The most common cue for nonadherence is the experience of a symptom. See *Section 5.4 - Managing Symptoms* for a list of HRT-related symptoms and *Section 7.3 - Adverse Effects* for CaD-related symptoms. Sometimes the participant will avoid taking study pills altogether when she feels that they are causing symptoms. Sometimes the participant will take pills sporadically when the symptoms change or worsen. Questions to ask about symptoms and resulting adherence problems are:
     - Frequency of symptoms.
     - Severity of symptoms.
     - Number of problems due to the symptoms.
     - Self-medication for the symptoms.

     Some participants attribute unrelated symptoms to the study pills, particularly in blinded studies. For example, a participant may claim that the pills are making her ear pain worse, when there is no known link between the ear pain and the active agent or placebo. Ask the participant direct questions about what she thinks causes the symptoms.
   - Emotions and cognitions. Many cues and reinforcers for adherence behavior are emotional in nature. Common emotions that may drive adherence are fear, worry, anxiety, concern, relief, and strong

conviction. Participants use these emotions as reasons to not take their pills (e.g., I was worried that the pills might make my recent illness worse) or as reinforcers (e.g., I felt much better after I stopped taking the pills). Stress and the resulting emotional reactions often interfere with adherence. Helping to organize a special event, such as a daughter's wedding, can be very stressful, and the many associated emotions and strains can result in poor adherence. Thoughts or cognitions (perceptions) can influence a participant's adherence and are often related to emotions. For example, if a woman believes that HRT causes breast cancer, she will also have fears about her own risk of breast cancer, and a belief that HRT is harmful. Ask about the participant's beliefs and thoughts regarding her study pills.

- Behaviors. Participants often use behavioral cues to remind themselves to take pills. When these behavioral cues fail, poor adherence can result. For example, if a participant takes her daily pill with her morning coffee, then she is likely to forget her pill on days when she does not have coffee. Ask the participant to identify the cues on both the days that she took the pills and on the days that she did not. Also ask her if something prevented her from responding to her normal cues on the days that she did not take the pills (e.g., distraction, disruption).

- Difficult situations. Often participants do not adhere to their pill-taking patterns when they experience a disruption in the flow of daily activities. Ask about several kinds of disruptions, including vacations, work disruptions, weekends and holidays, social events, shopping and day trips, illnesses, and problems of self and others. Discuss with the participant which of these are planned disruptions (e.g., weekends) and which are unplanned (e.g., health problems).

3. Identify solutions

Discuss the adherence problems and potential solutions with the participant. Match the solution to the nature of the problem. For example, if the problem is emotional, then discuss the emotions that get in the way of taking the pill. Use the categories of solutions below to discuss strategies for better adherence. Record your solutions and specific strategies on the *IAP Checklist*.

- Symptoms. Encourage the participant to deal with symptoms using methods that have worked for her in the past. Offer her new options if the ones she has used are not working. Reassure her that most symptoms are not signaling harm. Talk about the difficulty in a double-blind trial of not knowing what she is taking and assuming that the pills are causing all of the problems. Discuss with her the idea that aging produces changes in a woman's body and that potentially many of the symptoms she is experiencing might be due in part to these changes. Indicate that some of the symptoms may not go away, but they can occur "in the background" (be more tolerable) and not interfere with her daily life if you and she work together. Ask her if she thinks of these symptoms often or just once in a while. Ask her to identify methods of putting the symptoms "in the background" so that she can keep taking the pills and get the potential benefits from the trial.

- Emotions and cognitions. Deal with each specific fear, emotional reaction, or belief separately. Validate each reaction as normal and understandable and discuss each belief rationally. Be open about unknown findings, and correct misperceptions that she may have about the pills and associated health problems. Ask her if other things in her life have been difficult or problematic. Help her to understand that many different factors may be causing the emotional reactions that she attributes to the pill regimen. Ask her if she has a source of social support that can help her with difficulties. Ask her if she gets out of the house and sees friends and family. Discuss the fact that sometimes friends and family can be nonsupportive, and that the best sources of social support for her are ones that help but do not nag. Discuss strategies for obtaining support if needed.

- Behaviors. Discuss optional cues that can help the participants remember to take pills. These options include existing strategies (e.g., pill organizer) and new ones (e.g., asking a family member or friend to remind the participant on busy or non-routine days). Identify whether the participant has a consistent problem with forgetting, or whether the memory problem is specific to certain problem areas. For consistent memory problem, discuss her usual daily activities and how to fit the pills into these activities. For sporadic problems, identify the specific activities, days, and/or times that remembering seems to be a problem.

- Difficult situations. Classify the situations in which the participant has difficulty taking her study pills into planned and unplanned disruptions. Discuss and strategize about each specific type of disruption. For planned disruptions, help the participant identify a set of steps to use in the anticipated situations. For example, some participants take frequent day trips. These can upset her daily routine and can cause difficulty taking the study pills. However, these types of activities are mostly scheduled in advance and require just a few additional steps to make sure that pills are available and taken. Participants can choose a time to review their calendar weekly or monthly to make concrete plans for remembering to take pills. Unplanned disruptions are more difficult. These types of disruptions in daily routine are often not noted on the participant's calendar, and so planning ahead for each one is not an option. For some participants, however, these unplanned disruptions occur frequently and disrupt pill-taking behavior. Therefore, it is important that participants with frequent unplanned disruptions develop a general contingency plan for dealing with them. For example, the participant can keep 1-3 pills in her wallet, purse or glove compartment for emergencies, while leaving the bottle and pill organizer at home. Discuss strategies for always being prepared for the unexpected. Ask her for a step-by-step plan for being prepared for unusual or disruptive situations that she cannot control or anticipate.

4. Reinforce appropriate attributions

People sometimes set aside or forget motivators and commitments when they are faced with an immediate frustrating problem like symptoms or stress. Remind participants of the bigger picture as you progress through the IAP. Weave these comments into all of the above steps as appropriate. These categories of attributions or viewpoints will help increase adherence.

- Motivations. Remind the participant of her reasons for joining the trial and the skills that she currently possesses that can get her through the difficult parts. Examples include:
  - "I know that you are the kind of person that contributes her time to the WHI because you want to help others, and you certainly are by continuing to take your study pills."
  - "You have been really successful in the past (or in other situations) taking these pills. Let's figure out what you can apply from other situations to this one."

- Persistence. Tell the participant that you know she is committed to taking the pills and seeing WHI succeed. Examples include:
  - "It's wonderful that you can manage your study pills despite the annoyance of minor symptoms or hassles."
  - "Your persistence with this problem shows that you are highly motivated to do well in this trial."
  - "Your perseverance shows that you can really keep on track with the study pills."

- Coping. Indicate that the participant has the determination and skills to get through this difficult period. Examples include:
  - "Your ability to come this far is the direct result of your ability to solve tough problems."
  - "I can see by your diary [or our discussion] that you can really figure out this kind of problem."

5. Check for success

Discuss with the participant her progress and difficulties in trying out some of the strategies you both have identified. Note her progress on the *IAP Checklist*. See how the solutions worked in improving or ending the problem. Have the participant self-monitor again, if necessary, to see where problems have been resolved and where they still need attention. Keep in contact with the participant and repeat the steps above if the problem is not resolved.

Ending IAP Contacts

The IAP Coordinator decides when to end the contacts. The program might end because it is successful or because it will never be successful, in the judgment of the IAP Coordinator. Document the conclusion of the IAP on the *IAP Checklist*. If adherence activities have not been successful and the participant has changed her participation status, complete *Form 7 – Participation Status* (see *Section 17.2.2.1.4 - Ending Special Activities for HRT/CaD Retention Challenges*).

Reactivating IAP Contacts

Participants might develop different problems over time and therefore become candidates for the IAP more than once. Follow the procedures outlined above, even if the person has been in the IAP before. The IAP Coordinator should refer to previous IAP documentation for information about earlier adherence problems and strategies for managing those problems.

17.2.2.3 Documenting and Tracking Special Activities for HRT/CaD Retention Challenges

The following forms and reports may be useful in identifying which participants need special retention activities and documenting and tracking activities that have been initiated or completed:

- *HRT/CaD Medication Adherence (WHIP 1260)* – Use this report to identify which participants require special retention activities due to low adherence levels (i.e., less than 80%).

- *Form 10 – HRT Management and Safety* – This form is completed at each semi-annual visit to evaluate safety issues related to HRT use. Refusal to complete this form results in a participant's removal from the intervention. Item 13 on this form indicates that a participant needs to be enrolled in the IAP.

- *HRT Management Recontact (WHIP 0616)* – This form lists participants who need to be recontacted as indicated on *Form 10*. The report output indicates whether the needed contact is a one-month safety contact or an IAP contact.

- *Form 17 – CaD Management and Safety* – This form is completed at each annual visit to evaluate safety issues related to CaD use. Refusal to complete this form results in a participant's removal from the intervention. Item 11 on this form indicates that a participant needs to be enrolled in the IAP.

- *CaD Management Recontact (WHIP 1048)* - Use this report to identify which participants should be receiving IAP contacts, as indicated on Form 17.

- *IAP Checklist* and *IAP Participant Call Record* - Use these to document IAP activities.

- *Form 24 – Adherence and Retention Worksheet* - This form can be used to track retention activity, to identify which participants need further adherence/retention assistance, and to indicate when (i.e., date) future contacts should be made.

- *Member Adherence and Retention Activity Tracking (WHIP 1238)* – This report is used to track which participants have received retention/adherence contacts (based on *Form 24* data) and the date to conduct future contacts, as needed. The report can be sorted by member ID or name, retention problem (i.e., in which study component), or date for next contact.

17.2.2.4 Ending Special Activities for HRT/CaD Retention Challenges

When special adherence and retention strategies have been exhausted and the participant indicates that she is no longer willing to take her study pills and/or complete follow-up safety procedures (HRT and CaD) complete a *Form 7 - Participation Status* to reflect the change in status. If the participant decides to resume with intervention and/or follow-up activities that had been previously stopped, update *Form 7 - Participation Status* as appropriate to

indicate the current level of participation status (i.e., make sure that the participation status [intervention and/or follow-up status] indicated on Form 7 accurately reflects the level of participation she is currently willing to do).

Try to maintain the highest level of participation that the woman is willing to achieve. Even if she refuses to take her study pills, it is very important to try to keep her on a high level of follow-up status. Contact participants with less than full intervention status at least once a year throughout the study to see if they are willing to resume some or all aspects of their participation (see *Section 17.4.5 - Reactivation of Participants with Changes in Participation Status).*

17.2.3 Special Activities for DM Intervention Retention Challenges

This section includes information on identifying DM Intervention retention challenges, initiating special activities for retention challenges, tracking and documenting special activities, and ending special activities.

17.2.3.1 Identifying DM Intervention Retention Challenges

Retention challenges for DM Intervention are characterized by difficulty meeting Dietary Change goals and/or difficulty completing Dietary Change sessions. Refer to *Section 6.10 (including all subsections) – DM Intervention Participation* and *Section 6.11 (including all subsections) – Intensive Intervention Protocol (IIP)*.

17.2.3.2 Initiating Special Activities for DM Intervention Retention Challenges

The Group Nutritionist uses the Triage System for DM Intervention to set priorities for managing participants having retention challenges. The system categorizes participants into one of four adherence categories where Level 1 reflects high adherence and Level 4 reflects low adherence. Refer to *Section 6.10.7 – Triage System for DM Intervention.*

Difficulty Meeting Dietary Change Goals

The Group Nutritionist uses high intensity Intensive Intervention Protocol (IIP) procedures with Level 2 and Level 3 participants having difficulty meeting Dietary Change goals. Refer to *Section 6.11 – Intensive Intervention Protocol (IIP).*

Difficulty Completing Dietary Change Sessions

The Group Nutritionist most often uses low intensity Interrupted DM Intervention Participation procedures with Level 4 participants having difficulty completing Dietary Change sessions. However, the Group Nutritionist may use high intensity IIP procedures with Level 4 participants if CC resources support this level of effort. Refer to *Section 6.10.8 – Interrupted DM Intervention Participation Procedures*.

17.2.3.3 Documenting and Tracking Special Activities for DM Intervention Retention Challenges

The Group Nutritionist documents Intensive Intervention Protocol (IIP) contacts using *Form 64 – Individual Data Sheet* and progress notes. The Group Nutritionist tracks IIP contacts using the *IIP Triage & Tracking (WHIP 0444*) report. Refer to the following manual sections*: Vol. 2, Section 6.11 (including all subsections) – Intensive Intervention Protocol (IIP), Vol. 3 – Forms, Instructions for Form 64 – Individual Data Sheet, Vol. 5, Section 8.2 – DM Intervention Group Reports* and *Vol. 5, Appendix D – WHILMA Reports*.

The Group Nutritionist documents Interrupted DM Intervention Participation contacts using *Form 24 – Adherence and Retention Worksheet* and progress notes. The Group Nutritionist tracks Interrupted DM Intervention Participation contacts using the *IIP Triage & Tracking (WHIP 0444)* and *Member Adherence and Retention Activity (WHIP1238)* reports. Refer to the following manual sections: *Vol. 2, Section 6.10.8 (including all subsections) – Interrupted DM Intervention Participation Procedures, Vol. 3 – Forms, Instructions for Form 24 – Adherence and Retention Worksheet* and *Vol. 5, Appendix B.3.4 – Adherence and Retention Worksheet.*

17.2.3.4 Ending Special Activities for DM Intervention Retention Challenges

The Group Nutritionist stops special retention activities if the participant refuses all contact with the Group Nutritionist and other CC nutrition staff. Ideally, a non-nutrition CC staff member with retention responsibilities (e.g., retention specialist or designee) attempts to continue special retention activities when the participant refuses all contact with CC nutrition staff.

If the participant refuses all contact with CC nutrition staff and all special retention activities have failed, refer to *Sections 6.10.6.2.1 – Non-Participation* and *17.4 – Changes in Participation Status* for information about stopping intervention.

17.2.4 Special Activities for Follow-up Retention Challenges (CT and OS)

A participant becomes a follow-up retention challenge and requires special activities when she is unwilling to participate in follow-up activities, including visits (i.e., annual visits), phone calls, or mailings.

17.2.4.1 Identifying Follow-up Retention Challenges

Follow-up retention challenges are defined as follows:

- HRT/CaD Follow-up Problems: Follow-up retention challenges in HRT and CaD occur when a participant refuses phone and mail contacts during the follow-up period and/or refuses to come in for follow-up visits to complete the ongoing minimum safety requirements following randomization. Failure to meet minimum safety requirements will result in the participant's removal from active HRT or CaD intervention (see *Section 16.4.2 - Minimum Procedures Required for a CT Participant to Remain in Intervention*).

- DM Follow-up Problems: Follow-up retention challenges in DM occur when a participant (intervention or control) refuses phone and mail contacts during the follow-up period and/or refuses to come in for follow-up visits (see *Section 16.4.2 - Minimum Procedures Required for a CT Participant to Remain in Intervention*).

- OS Follow-up Problems: An OS participant who refuses phone and mail contacts during the follow-up period and/or who refuses to come in for the 3-year annual visit is a retention challenge and requires special retention activities.

17.2.4.2 Initiating Special Activities for Follow-up Retention Challenges

When a participant has been identified as a follow-up retention challenge, initiate any special retention activities available to help keep her on full follow-up. See *Section 16.4 - Follow Contact Problems for Annual (CT) and Third-Year (OS) Visits* for strategies on managing follow-up contact problems for annual (CT) and third-year visits. Refer to *Section 16.5.3 - CC Date Collection for Non-Respondents to OS Mailings* for procedures on initiating contact with OS participants who have not responded to data collection attempts by mail.

See also *Tables 17.3 - Reasons for Poor Retention and/or Adherence*, *17.4 - Strategies to Retain Full Participation in CT and OS*, and *17.6 - Examples of Retention Strategies* for ideas on ways to keep participants on full follow-up.

17.2.4.3 Documenting and Tracking Special Activities for Follow-up Retention Challenges

The following forms and reports may be useful in identifying which participants need special retention activities and documenting and tracking activities that have been initiated or completed:

- *Missed Scheduled Visit (WHIP 0799)* – This report lists all participants who do not have any encounters for their most previously scheduled visit (as per the *Member Visit Schedule Tracking* screen).

- *OS Enrolled Members Needing Clinic Follow-up (WHIP 1206)* – Lists OS participants who have not completed a *Form 33 – Medical History Update* following the mailed data collection contacts (during Year 1, 5, 7, or 9). These women require CC mail or phone follow-up to obtain a completed *Form 33*.

- *Form 24 – Adherence and Retention Worksheet* - This form can be used to track retention activity, to identify which participants need further adherence/retention assistance, and to indicate when (i.e., date) future contacts should be made.

- *Member Adherence and Retention Activity Tracking (WHIP 1238)* – This report is used to track which participants have received retention/adherence contacts (based on *Form 24* data) and the date to conduct future contacts, as needed. The report can be sorted by member ID or name, retention problem (i.e., in which study component), or date for next contact.

17.2.4.4 Ending Special Activities for Follow-up Retention Challenges

Special activities may be discontinued when one of the following occurs:

- The participant agrees to some level of follow-up participation.

- The participant requests no further contact from the CC.

Try to maintain the highest level of participation that the woman is willing to achieve. Even if she refuses to take her study pills, it is very important to try to keep her on a high level of follow-up status. Contact participants with less than full intervention status at least once a year throughout the study to see if they are willing to resume some or all aspects of their participation (see *Section 17.4.5 - Reactivation of Participants*).

If at the end of special activities, the participant's follow-up status has changed (e.g., activities have failed and she requests "no-follow-up"), complete *Form 7 - Participation Status* to indicate the change. See *Section 17.4.2 - Changing Follow-up Status* for guidelines and procedures on changing follow up status.

If a participant cannot be located, initiate a search to determine her current location (see *Section 17.3.1 - Initiating a Search to Locate Participants (Form 23)*).

17.3 Locating "Hard to Find" Participants

The term “hard to find” is used to designate a participant the CC has lost contact with and is searching for. WHILMA automatically updates the participant’s follow-up status to “lost-to-follow-up” as long as the participant is not “no follow-up” or “absolutely no contact,” and if:

- For CT – either no *Form 33* within 18 months or no *Form 23* with “found” box marked within 6 months
- For OS – either no *Form 33* within 24 months or no *Form 23* with “found” box marked within 12 months

17.3.1 Initiating a Search to Locate Participant (Form 23) (Required for Vital Status Searches)

If at any stage in the study a WHI participant misses a scheduled contact for an unknown reason, it is important for the CC to re-establish contact with the participant as soon as possible to ensure that the participant does not become lost to follow-up.

A search to locate the participant should be initiated in any of the following circumstances:

- A participant misses a clinic visit for an unknown reason and CC staff cannot make contact with the participant either by phone or by mail.
- A participant fails to return a mailed questionnaire and CC staff cannot make contact with the participant either by phone or by mail.
- CC staff have unsuccessfully tried to contact the participant by phone for a phone interview, and have been unable to make contact with the participant by mail.
- Mail sent to the participant has been returned to the CC because the participant is no longer at the address (and an updated address is not available) and the participant cannot be contacted by phone.
- A participant is listed on *WHIP 1591 – Participants Who Are Lost-to-follow-up and Participants Requesting No Follow-up.*

A search need not be initiated if the participant is known to be away (on vacation, for example) and will be reachable at the address and phone number listed in her file at a later date. The CC staff should exercise discretion in deciding how soon after a missed contact to begin efforts to locate the participant. In general, a search should be initiated on all participants whose whereabouts have not been established once the time window for the scheduled contact has ended.

To initiate a contact search to locate the participant, complete and data enter the top part of *Form 23 - Search to Locate Participant*.

17.3.2 Strategies to Locate “Hard to Find” Participants (Recommended)

CCs should develop their own forms and procedures for tracking attempts to locate participants once a *Form 23 - Search to Locate Participant* has been initiated. A record of attempts to locate the participant should be kept in her file (refer to *17.1 - Sample Form to Track Contact Attempts* for a sample form to keep track of contact attempts). Refer to *Form 23* for procedures on locating the participant and use it to record which steps have been taken to locate her.

Each CC should designate one staff member to be in charge of efforts to locate “hard to find” participants although this person may use other staff members to assist in locating participants with whom contact has been lost. The range of strategies used to trace participants, the sequence and frequency in which tracing attempts are carried out, and the amount of effort expended in locating hard to find participants should be decided by each CC, depending on local circumstances and accessibility of useful sources of information. However, all CCs are required to meet the overall retention goals.

In the process of tracing a participant, try to avoid inconveniencing persons from whom information is requested. Be particularly sensitive when making contact with personal contacts of the participant if it is suspected that she may be "hard to find" because she has died.

The following strategies may be used to trace missing participants:

- Attempt to contact the participant by phone. Repeat attempts on several occasions on different days and at different times of day, including evenings and weekends. If the participant is employed, try her work number as well as her home number. If the participant is not in, leave a message for her to call the clinic with the person who answers the phone or on the answering machine. If there is no answer after several attempts, the participant may be away on vacation; try again a few weeks later.
- If the participant's phone number has changed, try to obtain her new number from the phone book, directory assistance, or by using a reverse directory (e.g., Polk, Coles). If the participant has changed to an unlisted phone number, you may request that a supervisor from directory assistance contact the participant and ask her to call the CC.
- Attempt to contact the participant by mail. Send her a letter with "Address Correction Requested" printed on the envelope, requesting that she contact the CC.
- If the above is unsuccessful, send a certified letter to the participant's last known address requesting that she contact the CC.
- Contact personal contacts named in *Form 20 - Personal Information* by phone or by mail in order to obtain updated address and phone number information on the participant, and to confirm that she is not deceased.
- If attempts at contacting personal contacts and the physician are unsuccessful, try contacting neighbors or the current resident at the participant's last known address (using reverse directories).
- Check with state and local public agencies, and other sources listed on *Form 23 - Search to Locate Participant* as appropriate, including: state death records, local cancer registries (e.g., SEER), State Department of Motor Vehicles, local Social Security Office, and local voter registration records.

17.3.3 Ending the Search to Locate Participant (Required)

The search to locate the participant should continue until one of the following has occurred:

- you have contacted the participant;
- you have obtained updated phone number and/or address information;
- you have discovered that she is deceased;
- repeated attempts to contact the participant and her personal contacts using all strategies have been exhausted and you have failed to reach the participant, receive updated phone/address information, or determine that she is deceased.

This last criterion for ending a search will only apply once attempts to contact the participant have been repeated at intervals over a 6 month time period. When you have exhausted reasonably accessible avenues of inquiry for locating lost participants, close out *Form 23 - Search to Locate Participant* by indicating the search result status. Enter the date that the search is ended and the result of the search on *Form 23*, and data enter the form in WHILMA to close out the search.

If search attempts yield updated address or phone information, update the member screen in WHILMA.

Once contact is made with the "hard to find" participant and/or you have updated phone/mail information, contacts that she has missed should be rescheduled, if appropriate (See *Section 16.4 - CC Follow-up of Missed Contacts*). If upon re-establishing contact with the participant, she states that she is no longer willing to maintain full participation status in the study, begin retention activities (see *Section 16.4 - Follow-up of Missed Contacts).*

If the participant is found to have moved to an address far from the CC and is no longer able to attend clinic visits, her status should be changed to "no clinic visits" but follow-up by mail and phone should continue (See *Section 17.4 - Changes in Participant Status*). Participants who have moved and who no longer attend clinic visits may stay on intervention as long as the minimum safety procedures for their study component are carried out.

If the participant has moved to an address sufficiently close to one of the other CCs to be able to make clinic visits, arrangements should be made to transfer her to the nearest CC if she agrees (see *Section 17.5 - Transfer of Participants Between Clinical Centers*).

If search attempts yield information that the participant has died since the last contact, complete *Form 120 - Initial Notification of Death*, and process according to procedures outlined in *Volume 8 - Outcomes.*

The CCC will routinely request searches of the National Death Index for all participants with follow-up status "lost to follow-up" (see *Section 17.3.5 - Searches of the National Death Index*).

17.3.4 Procedures for Study Wide Vital Status Ascertainment (Required)

A. Definition of Vital Status

A participant's vital status is considered to be one of the three following categories: known to be alive, deceased, or lost-to-follow-up.

Deceased is defined as follows:

- *Form 120 - Initial Report of Death* or *Form 124 - Final Report of Death* completed.

Known to be Alive is defined as follows:

- Does not meet deceased criteria, and
- For CT participants: at least one of the following has happened:
  - a *Form 33* in the last 18 months, or
  - a *Form 23* in the last 6 months, with Item 4-Search Result, code 1 – "participant has been located" marked.
- For OS participants: at least one of the following has happened:
  - a *Form 33* in the last 24 months, or
  - a *Form 23* in the last 12 months, with Item 4-Search Result, code 1 – "participant has been located" marked.

WHILMA automatically updates the participant's follow-up status to "lost-to-follow-up" as long as the participant is not "no follow-up" or "absolutely no contact." Names appear on *WHIP 1591* under the following circumstances:

- CT – either no *Form 33* within 18 months or no *Form 23* with "found" box marked within 6 months.
- OS – either no *Form 33* within 24 months or no *Form 23* with "found" box marked within 12 months..
- "No follow-up" participants, when they meet the CT/OS criteria for "lost" (bullets 1 and 2 above). However, to ensure that participants do not fall off of reports, follow-up status remains "no follow-up."

Note: Participants with "no follow-up" status are only contacted/searched for annually.

Participants' names will not appear on *WHIP 1591* under these circumstances:

- *Form 120 – Initial Report of Death* and/or *Form 124 – Final Report of Death* has been data entered.
- Participants with "absolutely no contact" status.

Note: The lack of *Form 33* drives the definition of lost-to-follow-up. It is possible a participant has come into the clinic in the last 18 months and completed required clinic forms, excluding *Form 33*. By definition, this participant will be included on *WHIP 1591 – Participants Who Are Lost-to-follow-up and Participants Requesting No Follow-up* because outcomes data are missing. For this reason, CCs should make every effort to collect the medical information on *Form 33* each time they have a routine contact with a participant.

B. Procedures

1. *Vital Status Investigation (WHIP 1591)*

The CCC began distributing a new clinic-specific report, *WHIP 1591 – Participants Who Are Lost-to-follow-up and Participants Requesting No Follow-up*, for main and satellite sites, in January 2000. This report lists all CT and OS participants defined as Lost-to-Follow-Up (as defined in "Definition of Vital Status" above). The report includes the participant's ID, name, current vital status, last *Form 33* received date, last *Form 7- Participation Status* and *23 – Search to Locate Participant* information, and prior follow-up status. For each participant listed on the report, CCs are required to conduct a search to locate the participant.

WHIP 1591 – Participants Who Are Lost-to-follow-up and Participants Requesting No Follow-up also includes participants in the CT and OS who have a current follow-up status of "no follow-up," since Vital Status ascertainment needs to periodically occur for these women as well.

2. Conducting a search using *WHIP 1591 – Participants Who Are Lost-to-follow-up and Participants Requesting No Follow-up*

For each participant listed on the *WHIP 1591*, complete a search to locate the participant. The search to locate participant should include:

- Review of the participant's chart, including verification of phone number and retention documentation before making a contact.
- Review of *Vol. 2, Section 17 - Retention*, for a comprehensive review of retention strategies.

In general, use a six-month time period as a guideline for the search duration. For future searches, make every effort to conclude in time for the DSMB database freezes. (Notification of freeze dates are sent by the CCC.) However, do not compromise the search--if the search is on-going, do not close the search out. Continue to search until all sources are exhausted before you complete *Form 23* and close out the search.

3. Document search results on *Form 23 - Search to Locate Participant*.

Complete the forms based on the search results, as follows:

a. If participant has been in contact with the clinic in the last 18 months:
   - Document the contact information on *Form 23*:
     - Record the date you spoke or had contact with participant in Item 1-Initiation date;
     - Enter the current date in Item 4 - Date Search Ended.
     - Complete the rest of the form as appropriate.

b. If CC is in the process of searching for a participant:
   - Document the contact information on *Form 23*;
   - Attach documentation of the search to the *Form 23*;
   - Indicate the date you began the search in Item 2 - Initiation date on *Form 23* and continue searching for participant;
   - When the search is complete, record the search results and complete Items 4-6 - Date Search Ended, Search Ended By, and Search Result.

c. If participant is located (includes a participant who is deceased):
   - Document search on *Form 23 - Search to Locate Participant*;
   - Complete rest of *Form 23*. Mark code 1 - "Participant has been located." in Item 6 - Search Result. If participant is deceased, also complete *Form 120 - Initial Report of Death* and ask a proxy to complete *Form 33*, if possible;

- Update *Form 7* to change a participant's follow-up status by using the "prior status" listed on *WHIP 1591* unless a new follow-up status is negotiated directly with the participant.

Note: If a participant listed on the report completes a *Form 33*:
- and you have not initiated a *Form 23*, you are not required to complete *Form 23.*
- if you have initiated a *Form 23*, you must complete the *Form 23* and data enter it to close out the search, regardless of whether or not the participant completed a *Form 33*.

d. Participant is not located:
- Document search on *Form 23*;
- Complete rest of *Form 23*. Mark code 4 - "The participant could not be located" in Item 6-Search Result.

4. Document changes in participant follow-up status on *Form 7 - Participation Status*, if appropriate.

For any participant listed on *WHIP 1591*, you need to update the participant's follow-up status on *Form 7*, if:

- participant completes a *Form 33*, or
- you complete a *Form 23*, marking code 1 – "participant has been located" in Item 6-Search Results."

Note: If the participant was previously on "no follow-up," it is not necessary to change the follow-up status unless she indicates that she wants to change (i.e., resume or increase her study participation).

For participants who appear on *WHIP 1591* who have a follow-up status set to "lost-to-follow-up," based on the criteria described in *B.1 - Vital Status Investigation* above:
- When you find the participant alive (i.e., collect a *Form 33* or indicate "participant has been located" on *Form 23*), you need to change the follow-up status from "lost-to-follow-up" to her prior status listed on *WHIP 1591* unless a new follow-up status is negotiated directly with the participant. To do this, complete *Form 7*, indicating if the participant is on full, partial, custom, or no follow-up.
- When you find the participant is deceased, do not update her follow-up status on *Form 7*. Instead complete *Form 120 - Initial Notification of Death.*

5. Data enter the *Form 23, Form 7* and *Form 33* before the DSMB database freeze dates, when possible.

17.3.5 Searches of the National Death Index (NDI)

For participants with follow-up status "lost-to-follow-up", the CCC will periodically send in requests to search the National Death Index (NDI) to the National Center for Health Statistics, in order to determine whether "lost" participants have died since the date of last contact with the CC.

The information required for requesting searches of the NDI is abstracted from the WHILMA database by the CCC. In order to maximize the chance of a valid match and to minimize the chance of a false match being made, it is important to have as complete and accurate information as possible in the WHILMA database on items used in searches of the NDI. The following information is used when requesting NDI searches:

- Full name of the participant including first name, middle initial, and last name
- Maiden name (or father's surname)
- Social Security Number
- Date of birth
- Sex
- Race
- Marital Status

- Last known state of residence
- Age at death (estimate) or age when the participant was last known to be alive, based on CC records. The CCC will inform CCs of the results of NDI searches once they are available. If a search yields information that a participant has died, the CC will then be responsible for completing *Form 120 - Initial Notification of Death* and processing according to procedures outlined in *Volume 8 - Outcomes*.

The CCC may also make use of other national sources such as the Social Security Administration, Health Care Financing Administration (Medicare), US Post Office National Change of Address Tape, and credit bureaus to ascertain the vital status and/or updated address information of participants lost-to-follow-up, if resources permit.

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17.4 Changes in Participation Status

Participants are assumed to be on full participation in WHI, unless a change is indicated using *Form 7 - Participation Status*. Participation status is divided into intervention status and follow-up status (see *Form 7 - Participation Status)*. A participant's intervention status indicates the degree to which she is willing or safely able to participate in the WHI intervention(s) to which she was randomized. A participant changes intervention status if she becomes unwilling to participate in intervention activities or needs to stop the intervention for safety or other reasons, or if she decides to resume intervention activities that she had previously stopped. A participant's follow-up status indicates the degree to which she is willing or able to participate in the follow-up activities for her study component. A participant changes follow-up status if she becomes unwilling or unable to participate in full follow-up (e.g., if she refuses any of: CC visits, phone calls or mailing), if she cannot be located ("lost to follow-up"), if she has died, or if she decides to resume full follow-up after being on less than full follow-up (e.g., partial follow-up).

Participation status is used primarily to indicate what procedures the participant is willing and/or able to participate in. Temporary changes, such as the inability of a participant to come to a CC visit due to an illness or family problem, do not change her participation status. Similarly, ambiguous situations such as a participant failing to show up for a scheduled CC visit multiple times in general does not change her status unless she actually states that she is no longer willing to make CC visits.

Every effort should be made to encourage full participation throughout the study (see *Section 17.1 - General Activities*). Before a woman voluntarily changes status, specific retention activities should be conducted (see *Section 17.2 - Clinical Center Activities for Retention Challenges*) to alleviate the problem(s). If full participation is not possible, it is important to maintain some form of contact. A woman who insists on "dropping out" of the intervention should be encouraged to still come in for CC visits. For a woman who refuses CC visits, it is important to at least get agreement to contact her by mail and/or phone to follow her medical history.

Participants with less than full participation status are contacted periodically to determine whether or not they are willing to resume participation. Procedures for contacting and reactivating participants are in *Section 17.5. 4 - Reactivation of Participants with Changes in Follow-up Status*. *Form 7 - Participation Status* is also used to resume those aspects of participation that were formerly limited on *Form 7 - Participation Status.*

When a participant's follow-up status changes, complete a new *Form 7 - Participation Status*. When completing the form, there is no need to complete sections on the form other than the relevant parts that indicate how and why the status has changed.

17.4.1 Changing Intervention Status (Required)

Below are the definitions and procedures relating to changing a woman's intervention status for each study component. Intervention status only applies to CT participants.

17.4.1.1 DM Participants

Stop DM Intervention

This status only applies to those participants who are randomized to DM Intervention groups (i.e., does not apply to women in the DM comparison group).

Two circumstances warrant the "Stop DM intervention" designation:

1. The participant refuses all contact with the Group Nutritionist and other CC nutrition staff, and all special retention activities have failed. Retention activities must first be completed for these women (see *Section 17.2.3 – Special Activities for DM Intervention Retention Challenges)*.

2. The participant was removed from active DM Intervention participation by CC staff due to unresolved symptoms. Retention activities are not required.

A participant classified as "Stop DM Intervention," must also be removed from her current DM Intervention group assignment (see *Vol. 5 - Data System, Section 8.1.3 - Assigning and Removing Participants from a DM Intervention Group).*

Exceeding a fat gram goal is not a reason to change DM Intervention status. Refusal to come to CC follow-up visits or to fill out any or all forms is not a reason to "Stop DM Intervention." Because there are no required safety procedures for DM participants, women who refuse assessment procedures may continue intervention activities.

Resume DM Intervention

Use this classification if the participant agrees to actively participate in DM Intervention (see *Section 6.10.6.2.2 – Active Participation*), after having been previously classified as "Stop DM Intervention." Assign the participant to her previous or a new Dietary Change group (see *Vol. 5 - Data Systems, Section 8.1.3 - Assigning and Removing Participants from a DM Intervention Group).*

17.4.1.2 HRT Participants

Stop HRT Intervention

This does not include going off or on HRT pills while you are trying to resolve symptoms (use *Form 54 - Change of Medications* if there are changes in HRT study pills schedules or dosages). Low adherence (not consuming the appropriate number of HRT pills in the time between follow-up contacts) is not a reason for changing HRT intervention status (instead, initiate the Intensive Adherence Program for these participants - refer to *Section 17.2.2.2.1 – Intensive Adherence Program*).

The circumstances warranting the "Stop HRT Intervention" status are:

1. The participant is no longer willing to take her HRT study pills and retention activities have failed. Retention activities must first be completed for these women (see *Section 17.2.2 – Special Activities for HRT and CaD Intervention Retention Challenges*).

2. The participant refuses any of the safety procedures, and retention activities to maintain these safety procedures have failed. The safety procedures required to remain on HRT Intervention are described in *Section 16.4.2 - Minimum Procedures Required for a CT Participant to Remain in Intervention*. If the participant, or her proxy (if she is on proxy follow-up), refuses both CC visits and phone calls, then she must be changed to "Stop HRT Intervention" because she cannot meet the safety procedures.

   Note: retention activities must be completed before a participant's status is changed due to reasons 1 or 2 above.

3. The participant was removed from HRT pills by CC staff due to unresolved symptoms or an adverse event that necessitates removing her from the intervention permanently. Refer to *Section 5.5.4 - Health Problems Requiring HRT Termination* for a list of adverse events. These women should not have retention activities initiated.

Be sure to retrieve study medications from women classified as "Stop HRT Intervention" (see *Section 17.4.4 - Retrieving Study Pills [HRT and CaD]*). Indicate the date the participant stopped taking her pills (if known) on *Form 7*. If the date is not known, record the contact date.

Resume HRT intervention

Use this classification if the participant indicates she is willing to resume taking study pills after having previously been classified as "Stop HRT Intervention."

17.4.1.3 CaD Participants

Stop CaD Intervention

Low adherence (not taking the appropriate number of CaD pills in the time between follow-up contacts) is not a reason to classify a participant as "Stop CaD." (Instead, initiate the Intensive Adherence Plan described in *Section 17.2.2.2.1 - Intensive Adherence Program* for these participants.)

The circumstances warranting a "Stop CaD Intervention" status are:

1. The participant is no longer willing to take the CaD study pills and retention activities have failed (see *Section 17.2.2 – Special Activities for HRT and CaD Intervention Retention Challenges*).
2. The woman refuses to complete *Form 17 - CaD Management and Safety Interview* (at a CC visit or by phone or by proxy respondent) annually and retention activities have failed. The safety procedures required to remain on CaD Intervention are described in *Section 16.4.2 - Minimum Procedures Required for a CT Participant to Remain in Intervention*. If she refuses *Form 17 - CaD Management and Safety Interview*, she is not given any more CaD study pills.

   Note: Retention activities must be completed before intervention status is changed due to the above reasons.
3. The participant was removed from CaD study pills by CC staff due to unresolved symptoms or a adverse event that necessitates removing her from the intervention permanently (refer to *Section 7.3.3.1 - Management of Major Adverse Effects*). These women should not have retention activities initiated.

Retrieve study medications from women classified as "Stop CaD" (see *Section 17.4.4 - Retrieving Study Pills [HRT and CaD]*). Indicate the date the participant stopped taking her pills (if known) on *Form 7*. If the date is not known, record the contact date.

Resume CaD Intervention

Use this classification if the participant indicates she is willing to resume taking CaD study pills after having previously been classified as "Stop CaD Intervention."

17.4.2 Changing Follow-up Status (Required)

Follow-up status refers to the participant's ability or willingness to participate in CC visits, phone calls and/or mailings for the WHI assessment forms and procedures. Follow-up status applies to all participants (CT and OS). Below are the definitions and procedures relating to change in follow-up status.

17.4.2.1 No follow-up

"No follow-up" status is used when a CT or OS participant wants no follow-up (no CC visits, no phone and no mail contact), and retention activities have failed. Retention activities must be conducted before changing status to no follow-up. For HRT and CaD participants, WHILMA will automatically set the intervention(s) to which the woman was randomized to "stop." If she insists on no follow-up, she must stop HRT and CaD study pills (for safety reasons), and study pills should be retrieved (see *Section 17.4.4 - Retrieving Study Pills [HRT and CaD]*). "No follow-up" status does not impact DM intervention status and DM dietary change participants may continue to attend DM sessions.

Only participants who verbally refuse follow-up should be classified as no follow-up. Failure to participate (i.e., consistent failure to show up for CC visits) should not be used to classify a participant as no follow-up.

Contact the no follow-up participants periodically to see if they are willing to resume contact. When a participant specifically states that she will not tolerate further contacts, change her status to "absolutely no follow-up" and do not attempt further contacts.

17.4.2.2 Partial follow-up

Partial follow-up means that the woman is not able or willing to continue one or two of: CC visits, phone and mail contact. If she is unwilling to continue CC visits, she must have retention activities. If she is unable to attend CC

visits because she has moved or is seriously ill, retention activities are decided on by the CC. For a woman who has moved near another WHI CC, see *Section 17.4.5 - Transfer of Participants Between Clinical Centers.* If she has stopped both CC visits and phone contact and she is in the HRT and/or CaD intervention, she must stop HRT and/or CaD study pills (for safety reasons) (see *Section 17.4.4 - Retrieving Study Pills [HRT and CaD]*). For these women, WHILMA will set "HRT intervention" and/or "CaD intervention" to stop. Otherwise, "partial follow-up" women should be encouraged to stay on intervention. OS women who refuse the year 3 CC visit do not need to be classified as "No CC visits". Stopping DM intervention sessions only is not included as "No CC visits."

17.4.2.3 Proxy follow-up

If a woman can no longer communicate, for example, due to stroke or dementia, she may, if willing, continue in the WHI through a proxy respondent, usually one of her personal contacts. The order of priority for selecting a proxy respondent is: 1) spouse or partner; 2) nearest relative; 3) friend; 4) physician. On *Form 7 - Participation Status*, indicate "proxy follow-up" and identify the proxy who will be contacted. Participants on proxy follow-up may continue on intervention if the minimum procedures are followed. (See *Section 16.4.2 - Minimum Procedures Required for a CT Participant to Remain in Intervention.)* Specifically, a participant on HRT or CaD study pills on proxy follow-up must have her proxy approved (see *Section 16.7 - Follow-Up by Proxy).* If the participant will not remain on intervention, check the appropriate "stop intervention" box(es). Also check any appropriate boxes: no CC visits, no phone calls, and/or no mailings.

17.4.2.4 Custom follow-up

Use for special circumstances, such as refusal of specific forms or procedures (e.g., blood draws). Also check any appropriate boxes: no CC visits, no phone calls, and/or no mailings.

17.4.2.5 Lost to follow-up

This status is used when a participant's location (i.e., address and/or phone number) cannot be determined and attempts to locate her over at least a six month period have failed (see *Section 17.1 - Locating "Hard to Find" Participants* and *Form 23 - Search to Locate Participant*) and she has had no contact with the CC for at least one year. *Form 23* must be completed before a participant can be classified as lost to follow-up. When a participant has been classified as lost to follow-up, WHILMA will automatically change the appropriate intervention status to "stop."

17.4.2.6 Deceased

When a woman has died, complete *Form 7 - Participation Status* and *Form 120 - Initial Notification of Death.* WHILMA will automatically change the appropriate intervention status to "stop." See *Volume 8, Section 2 - Outcome Identification, Ascertainment, and Documentation* for the remaining procedures.

17.4.2.7 Absolutely no follow-up

All WHI women, even those currently classified as "no follow-up," should be periodically contacted so that they may reconsider participation in follow-up activities. "Absolutely no follow-up" means a woman should never again be contacted about participating in follow-up activities. This classification should be reserved for women who are hostile to WHI and unlikely to change. This classification requires PI approval.

17.4.2.8 Full follow-up

Use to indicate/resume full follow-up (mail, phone, and CC visits).

17.4.3 General Steps in Changing Participant Status

The initial indications that a participant wants to or should change intervention status can come from a number of sources: the participant, a family member, or CC staff. The general steps are:

- Identify the problem — What aspects of the participant's WHI participation does the participant or CC staff want to change? What are the reasons?

- Determine if retention activities need to begin, based on guidelines in *Sections 17.4.1 - Changing Follow-up Status (Required)* and *17.4.2 - Changing Follow-up Status*. If so, set up a time for CC staff to begin retention activities. If, following the retention efforts, the participant still requires a change in participation status, complete *Form 7 - Participation Status.*

- Determine if a search for a lost participant needs to begin. If so, complete and data enter the top part of *Form 23*. Complete *Form 23 - Search to Locate Participant* within 6 months. If the woman still has not been located, complete *Form 7 - Participation Status* to indicate "lost to follow-up."
- Directly complete *Form 7 - Participation Status* when neither retention activities nor a search for lost participants is needed.
- Ask the participant to return all study medications, if appropriate (see *Section 17.4.4 - Retrieving Study Pills [HRT and CaD]).*
- Complete the remaining procedures (see *Sections 17.4.1 - Changing Intervention Status (Required)* and *17.4.2 - Changing Follow-up Status (Required)*).
- Thank the participant for her WHI activity to date.

As noted above, when a problem with participant status has been identified, one of three forms is entered: *Form 23 - Search to Locate Participant* (upper part), *Form 24 – Adherence and Retention Worksheet* or *Form 7 - Participation Status*. In this way, those women with less than full participant status can be tracked.

17.4.4 Retrieving Study Pills [HRT and CaD]

Old study pills should be retrieved and new pills not given when:

1. A participant no longer is willing to take study pills and retention activities have been completed.
2. A participant refuses a required safety procedure (see *Section 16.4.2 - Minimum Procedures Required for a CT Participant to Remain in Intervention* for safety procedures). In such a case, old pills should be retrieved before retention activities have begun.
3. A CC staff member removes a participant from intervention due to a termination event or due to unresolved symptoms.

Make concerted attempts to retrieve all old study medications from the participants when they are classified "Stop HRT or CaD intervention." If possible, send a postage-paid envelope to the participant to return pills. If the participant does not return the medications, ask the participant to estimate the number of pills remaining and then to discard them. Enter pill count via WHILMA. If a participant who has stopped HRT or CaD intervention later requests reactivation, make clear to the participant that she should not take medications from previously dispensed bottles.

17.4.5 Reactivation of Participants with Changes in Participation Status

Reactivation is the procedure by which participants who have changed their intervention or follow-up status are re-contacted to increase their follow-up activity or to obtain follow-up information.

17.4.5.1 Purpose

The purpose of reactivation is to:

- Resume CC visits for participants who have previously asked to have no CC visits
- Return participants to their routine follow-up schedules
- Resume some form of follow-up contact for participants who have previously elected to have no follow-up or who have been lost to follow-up

- Resume intervention for eligible participants who previously had stopped intervention (either voluntarily, because of a refusal to complete safety monitoring procedures, or because of an illness event that necessitated stopping intervention)

All randomized participants will be included in the final clinical trial data analysis ("once randomized, always analyzed"). Thus, ensuring that WHI participants stay on their intervention and continue appropriate follow-up contacts is important to maintain and detect potential effects of the intervention. Retention problems may also dilute any true difference between treatment groups. Thus, participants who change their follow-up or intervention status will be allowed, and even encouraged, to return to active participation in the study whenever feasible.

17.4.5.2 Eligibility for Reactivation

All participants who have stopped their intervention are eligible for reactivation of intervention, except those who were removed from intervention because of specific health conditions or events that necessitate stopping intervention (see *Sections 5 - HRT* and *7- CaD*) or for whom a specific request was made by their personal physician to stop intervention (unless their physician has since allowed their return to the study).

All participants who have less than full follow-up status are eligible for reactivation of activities. Do not contact participants for reactivation if they have elected "no follow-up" until at least one year has passed since their last contact of any kind. You may reactivate these participants, however, if they initiate the process and are otherwise eligible.

When a participant changes her follow-up or intervention status, the CC staff records the reason on *Form 7 - Participation Status*. Use this information and any other information available from the participant's file to determine whether it is appropriate to encourage reactivation. For future reference, mark the charts of no-contact participants indicating whether they are eligible for reactivation.

CT participants who want to reactivate and who have elected no follow-up or no intervention for one year or more must come to the CC for a visit (see *Section 17.4.5.3.1 - Reactivation from No Follow-Up or Stop Intervention Status)*. If their change in follow-up or intervention status has been for less than one year, they may be reactivated by phone.

17.4.5.3 Reactivation Approaches (Recommended)

17.4.5.3.1 Reactivation from No Follow-Up or Stop Intervention Status

Each time an eligible "no follow-up" or "stop intervention" status participant is contacted by mail or phone, she should be offered the opportunity to resume CC visits. Her response to this solicitation should be noted in the contact notes in her participant file. If she indicates that she might be interested, discuss the possibility with her by phone or in person and explain what would be needed (annual visits, routine phone contacts, becoming active in intervention) without offending or harassing her. Ask if concerns have changed since the last contact. Tell her that her contribution to the study so far is appreciated.

If prompted or requested by the participant, offer that some aspects of the visits may be modified if it would make continuing participation easier. Examples of these modifications may be:

- Convenient appointment days and times
- Annual visits instead of semi-annual
- Help with filling out forms during the visit
- No blood draw
- No bone densitometry
- Group follow-up, if available

- Help with transportation, if available
- Free, safe, or more convenient parking, if available
- Security assistance, if available

When a participant, who has previously requested no phone or visit follow-up, shows interest in returning to the study, schedule reactivation as soon as possible; do not wait for the next usual contact window. Proceed with reactivation following the guidelines in *Section 17.4.5.4 - Reactivation Visit.*

- For a participant who has had no phone or in-person contact for less than one year, schedule a telephone appointment, if possible.
- For a participant who has had no phone or in-person contact for one year or more, schedule a reactivation visit, if possible. Offer directions and a map to the CC, if needed.
- Ask the participant, "*Do you have any questions that I can answer now?"* Encourage her to call if she has any questions before the telephone appointment or CC visit. Give the CC phone number to the participant.
- Thank the participant for her time, tell her that you enjoyed talking with her and that you hope to talk to her or see her on the scheduled date.

If the participant indicates she is not interested in returning to full follow-up or intervention status, tell her that it is important that WHI maintain contact with her to meet study goals, regardless of whether she takes her study pills or follows the dietary change program.

17.4.5.3.2 Reactivation From No Follow-Up Phone Contacts

At each mail contact with a participant who has elected no phone contacts, include a solicitation to resume follow-up activities and note her response on the contact notes in the participant's file. If she indicates that she might be interested, discuss the possibility with her by phone or in person and explain what would be needed (annual visits, routine phone contacts, becoming active in intervention) without offending or harassing her. Ask if concerns have changed since the last contact. Tell her that her contribution to the study so far is appreciated.

If prompted or requested by the participant, offer that some aspects of the visits may be modified if it would make continuing participation easier (see examples above).

17.4.5.3.3 Reactivation From No-Contact Mailing (Recommended)

Telephone the participant if she responds to a mailed solicitation to rejoin the study or phones the CC to indicate she is interested in rejoining the study.

Use the following guidelines:

- Keep the tone of the phone call conversational: warm, friendly, informative, and not rushed.
- During the phone call, determine what information is applicable to the participant.
- Have the participant's chart in front of you while you are making the call. Review the chart for the participant's name, date of last contact, and reason(s) for becoming no-contact.

An example of what you might say is:

"May I speak with Mrs./Ms./Miss (participant)? Hello (participant), this is (your name) from the Women's Health Initiative at (institution name). Do you have a few minutes to talk with me?" If no, schedule a time for the call.

"Thank you for returning the postcard we sent you. I received it recently and am happy you are interested in rejoining the study. You are a valuable part of the national effort to answer important questions about women's health.

"Based on our information, you were last in the clinic in (last contact month and year)."

Follow the steps described in *Section 17.4.5.3.2 - Reactivation from No Follow-Up Phone Contacts*.

17.4.5.4 Reactivation Visit (Recommended)

The reactivation visit is designed to follow the flow of regular follow-up visits, if acceptable to the participant. Complete the same forms and procedures as you would for the routine follow-up contact, if possible.

Conduct the contact that is closest to the visit target date. If the reactivation visit date is closest to the semi-annual contact target date, do a semi-annual visit (but use your judgment about whether a semi-annual mail and/or phone contact would be more acceptable to the participant). If the reactivation visit date is closest to the annual visit target date, do an annual visit.

17.4.5.4.1 Preparation (Recommended)

The preparation for a reactivation visit is similar to that for a routine follow-up visit. Determine whether the participant has signed the current version of the appropriate consent form(s) (i.e., have participants been reconsented since this participant changed her status). If not, put two copies of the appropriate consent form(s) in the participant's file.

17.4.5.4.2 Conducting the Reactivation Visit (Recommended)

Follow the general procedure for conducting the appropriate type of visit (see *Section 16.2. - Semi-annual Contact* or *Section 16.3 - Annual (CT) and Third-Year (OS) Visits*), including the modifications below. Use judgment as to how much to include in the initial reactivation visit, because some women may need more reassurance before fully participating (some participants may need a series of visits before agreeing to fully participate).

- Informed consent interview: Begin the interview by re-introducing yourself and the study to the participant. Remind the participant of the requirements of the study as stated on the consent form. Consider whether reconsent procedures are needed and/or if they should wait until the second reactivation visit. Have the participant sign a new consent form, if appropriate. Give a copy to the participant and file the signed consent form in the participant's file.

- Medical history and personal information updates: Obtain updated medical, health, and personal information covering the period between the participant's last contact with the CC and the current visit. This information should be documented on *Form 33 - Medical History Update* and *Form 20 - Personal Information*.

- Procedures: A reactivated participant may generally be less compliant than the average participant. Be sensitive to her concerns in order to maximize further WHI involvement. Discuss with her the importance of following the WHI protocol, even though she may refuse. It is better to allow the participant to decline one particular activity (e.g., blood draws), rather than lose her entirely.

- Dispensing study pills: Do not give study pills to any reactivating participant who is unwilling to agree to appropriate safety procedures. Other procedures are also important to study goals and should be performed unless the participant strongly opposes them. After you determine the next visit appointment date, calculate how many bottles of study pills to give to the participant. If the scheduled visit is less than six months away, give the participant one bottle of HRT and two bottles of CaD, as appropriate. If the visit is more than six months away, dispense two bottles of HRT and four bottles of CaD. Follow the usual study pill dispensing documentation procedure as outlined in *Section 15.4. - Medication Dispensing*.

- Scheduling future visits: Discuss with the participant the contact schedule in her file. If the current window for annual and semi-annual visits is inconvenient, you might modify the schedule slightly to accommodate the reactivated participant. Schedule the appropriate semi-annual or annual visit in the next visit window.

17.5 Participant Transfers Between Clinical Centers

During the course of the study, it may become more convenient for a participant to attend a CC other than the one that recruited her into the WHI study, and a participant may request a transfer to a more convenient CC. These transfers occur at the discretion of CC staff and are dependent on the feasibility of the transfer. For the purpose of participant transfers between clinics, satellite CCs are considered to be separate from their main CC, and the same policies and procedures apply to transfers between main and satellite CCs as apply to transfers between other CCs.

The primary concern when considering and carrying out participant transfers should be what is best for the participant and the study. The transfer process should be a positive experience for the participant and staff, yet still address study adherence and retention concerns. The responsibility for facilitating a smooth transfer is shared between the **originating** and **receiving** CCs. Both CCs must approve the transfers. If either CC is having difficulty with completing the process in a timely manner, referral to the Principal Investigator or designee may be appropriate.

Both the originating and receiving CCs must sign *Form 22-Participant Transfer* and submit it to the CCC before the CCC will initiate a transfer of data. When the CCC implements the data transfer, all of the participant's WHILMA records are moved from the originating CC's database to the receiving CC's database. That is, the originating CC will have no record of the participant ID, name, or other personal identifiers in its WHILMA database. The receiving CC will be responsible for any data changes, outcomes, or other tasks in WHILMA.

The following procedures are guidelines for CCs to use in communicating with each other during the transfer process.

Originating CC (see *Section 17.5.1 – Transfer Team Procedures [Originating CC]*):

- Participant makes an initial contact with the originating CC to tell staff that she has moved or will be moving. For information on appropriate considerations when a participant makes the initial contact about a transfer with the receiving CC, see *Section 17.5.2 – Transfer Team Procedures* (Receiving CC) under the heading "Participant Contacts Before Transfer Procedures Initiated."
- Based on information obtained from the participant, the originating CM and/or transfer team decides on the feasibility of transferring this participant to another CC and identifies the receiving CC.
- The Clinic Manager (CM) "transfer point person" and/or "transfer team" (see below under "Communications") identifies a CC staff person to make the next contact with the participant. This staff person contacts the participant to get further details about her move to facilitate completing the *Form 22 – Participant Transfer*. This step may occur at the same time that the participant initially contacts the originating CC about her move.
- The CM contacts (by email, fax or phone) the receiving CM to provide information about the impending transfer and to inform the receiving CC that basic documentation about the participant is being sent. Basic documentation to send to the receiving CC includes a copy of *Form 22 – Participant Transfer* (with originating CC information filled out) and reports. The originating CM may forward the *Form 22 – Participant Transfer* to the receiving CM for information, but should not sign Part I and initiate the formal transfer procedure until the participant has moved.

Receiving CC (see *Section 17.5.2 – Transfer Team Procedures [Receiving CC]*):

- Receiving CM is notified by the originating CM and receives basic documentation (see above) about the participant. Receiving CM acknowledges receipt of the information to the originating CM and identifies what steps have been or will be initially taken.
- CM and/or transfer team reviews the information, identifies an appropriate CC staff person to contact the participant, and identifies the next steps in the process.
- The appropriate CC staff contact person contacts the participant to establish if the participant is able and willing to come to the CC for visits.

- The receiving point person completes the *Form 22 – Participant Transfer*, stating that the CC agrees to accept the transfer, and sends it to the originating point person. The *Form 22 – Participant Transfer* sent to the originating CC also includes a request to send a:
  - copy or original of the participant's entire chart, including any archived sections
  - signed medical release from the participant giving the receiving CC permission to receive full CC documentation
  - sheet of participant labels
  - completed *Form 22 – Participant Transfer* signed by the originating CM.

Concluding the Transfer Process (see *Section 17.5.3. – Procedures to Finalize Transfer [Originating/Receiving CC]*):

- The originating CM sends the receiving CM the documents identified above.
- When the documents are received, the receiving CM faxes the last page of *Form 22 – Participant Transfer* to the CCC Data Coordinator.

The CCC Data Coordinator then enacts the WHILMA database transfer and informs both the originating and receiving CCs that the transfer has been completed.

Although there is no limit to the number of times a participant is allowed to transfer between CCs during the course of the study, transfers are intended to be used only for permanent (or long term) relocations of participants. Participants who will be moving closer to another CC for a limited period (less than one year), or seasonally (e.g., "snowbirds") should not be transferred.

Communications: Because communications between the originating and receiving CC is crucial to the transfer process, the originating and receiving CCs should each establish:

- a "transfer team" (e.g., CM, LN, CP, DC, OCS, retention or other staff)
- appropriate local guidelines for handling a participant transfer

The originating CM should then contact the receiving CM, provide all pertinent information about the participant and her need to transfer, and continue to follow-up with the other CM until the transfer is complete.

The CM at both CCs may also designate specific staff for contacting the participant about an impending transfer. The following are some component-specific considerations for identifying this participant contact person, as appropriate, at both the originating and receiving CCs:

- Clinic Manager or appropriate retention staff person for Observational Study or DM Comparison participants.
- Lead Nutritionist (LN) (or appropriate Group Nutritionist) for DM Intervention participants.
- Clinic Practitioner for HRT or CaD participants. Note that some CCs may designate CC staff other than the CP for CaD+DM participants.
- Staff person based on individual bonding (or anticipated bonding) with the participant may be most appropriate for participants in two or more of the Clinical Trials.

Timelines: Establish appropriate time frames for completing each step of the transfer process. Complete the steps of the transfer process quickly (e.g., the receiving CC should formally acknowledge the initial contact from the originating CC within one week of that contact). Once the receiving CM is notified by the originating CM of a transfer request and receives basic information, an acceptance or denial of the transfer should be communicated to the originating CM in a timely manner (less than 1 month). The length of time for completing the transfer process may vary because of the circumstances of each transfer (but should occur within a three month period). Send all information and documents to the receiving CC before the transfer participant's first clinic visit at the receiving CC.

Transfer Forms: The originating CC formally initiates the transfer process by completing all available information and signing Part I of *Form 22 – Participant Transfer*. The receiving CC completes and signs Part II of the *Form 22 – Participant Transfer* and faxes to the originating CC to complete Part III. The originating CC completes Part III and sends the completed *Form 22 – Participant Transfer* with the original or copied participant file to the receiving CC. The receiving CC faxes the completed *Form 22 – Participant Transfer* to the CCC Data Coordinator to complete the transfer.

17.5.1 Transfer Team Procedures (Originating CC)

The originating CC CM and/or transfer team establishes that a participant desires to be transferred to another CC (and a transfer seems appropriate) before an initial contact with the receiving CM. During this initial contact, the two CMs should discuss if it is appropriate for the CC to receive the transfer or if another CC is in a better location for the participant. The originating CC transfer team should be familiar with the participant's status to appropriately discuss and answer any questions for the receiving CC (e.g., contact information, previous transportation or attendance concerns, date of the proposed transfer).

Nutrition: If the participant is in the DM Intervention, the LNs (or appropriate Group Nutritionists) from both CCs should discuss the logistics of the transfer, schedule of classes available, and how to quickly involve the participant with the receiving CC. Discuss any logistical problems, such as transportation.

Have the appropriate originating CC nutrition staff person (e.g., LN for a DM intervention participant) conduct an exit interview with the participant. Run the final Individual Progress Report (*WHIP 0428*) and enter an end date for the participant in her originating DM intervention group in WHILMA.

It is highly recommended that an appropriate retention staff person at the receiving CC make the initial contact with DM Comparison transfer participants to enhance retention.

HRT/CaD: The originating CP (HRT, CaD) or other appropriate staff person (CaD) should be the initial person to contact the participant to initiate the transfer. Provide the participant with an adequate supply of study pills (not exceeding the usual limit) to last through the transfer process after the originating CC confirms that appropriate safety procedures, such as mammograms, are current. Have the appropriate originating CP contact and discuss the transfer with the receiving CP by email or phone. Review the participant's case, including information such as bleeding history, other symptoms or complaints, endometrial aspiration results, outstanding referrals or follow-up evaluations, adherence issues, step-down regimens, and alternative open label regimens with MPA or CEE.

The originating CC should review the participant's chart, noting the following:

- Date of next target contact and visit type (HRT, CaD)
- History and outcome of any Intensive Adherence Programs (HRT, CaD)
- Any safety issues or problems identified on any previous *Form 10 – HRT Management and Safety Interview/Form 17 – CaD Management and Safety Review* and dates of last follow-up (HRT, CaD)
- Date of randomization (HRT, CaD)
- Participation status as identified on *Form 7 – Participation Status* (HRT, CaD)
- Last two adherence rates (HRT, CaD)
- Any clinical problems or alerts identified on reports (HRT, CaD)
- Any outstanding follow-up tasks or when next are due (HRT, CaD)
- Any other information which you feel would be helpful to the receiving CC (HRT, CaD)
- Hysterectomy status (HRT)
- Date of screening EA and results (HRT)

- Any symptom (e.g., breast tenderness, bleeding, constipation, etc) that the participant may have experienced (HRT)
- Any altered dosages as identified on *Form 54 – Change of Medications* (HRT)
- Whether or not unblinding has occurred. (If so, a copy of the consulting gynecologist's records should be sent to the new CC's consulting gynecologist.) (HRT)
- Results and date of last mammogram (HRT)
- Results and date of last breast and pelvic exam and Pap smear (if applicable) (HRT)

The originating CP should conduct a "close out" interview with the participant, including:

- Date of departure
- New address and phone number of participant, if possible
- Assessment of pill supply and whether the participant needs another bottle dispensed to last her until her contact with the receiving CC
- Information on relevant receiving CC's staff names and phone numbers with information on when her next target contact is due
- (Optional) Any comments or suggestions from the participant on how to improve originating CC interactions with participants

Schedule a telephone call with the receiving CP or responsible staff to discuss the above information.

Data: Enter into WHILMA all data collected at the originating CC before sending the *Form 22 – Participant Transfer* is sent to the CCC. This includes all forms and any specimen or test results that have been done at the originating CC. Close out DM intervention participants from their originating CC intervention group. Study pill bottles dispensed to the participant do not have to be collected by the originating CC (unless you are doing a pill collection before dispensing more study pills to cover the transfer process time). Adherence on the current study pill bottle will be collected at the receiving CC once the transfer has been completed.

Reports: The *Form 22 – Participant Transfer* instructs the originating CC to run the following reports and fax them to the receiving CC:

- Personal Information Change Request (*WHIP 0441*)
- Missed Tasks at Visit (*WHIP 0618*) for CT participants for the last two annual visit contacts
- Members Outcomes Status (*WHIP 1215*) for CT and OS participants
- HRT/CaD Medication Adherence (*WHIP 1265*) for HRT and/or CaD participants
- Individual Progress report (*WHIP 0428*) for DM intervention participants
- Participant Contact Schedule (*WHIP 0472*)

Outcomes: All participant data, including outcomes data, disappear from the originating CC's database once a transfer is complete. Therefore, promptly enter completed outcomes tasks into WHILMA. Make every attempt to investigate, adjudicate, and close pending adjudications before a participant is transferred.

If an outcome is under investigation when the participant transfers, the receiving CC will complete the investigation and adjudication process. To ensure pending outcomes are investigated appropriately, it is recommended that the originating OCS contact the receiving OCS and discuss the status of pending investigations.

When one clinic begins an outcomes investigation and another completes the investigation and/or adjudication, simplify the transition by considering a "natural" stopping point, complete a particular outcomes task, key enter the appropriate information, and stop. Suggested stopping points include:

- *Form 33-Medical History Update* is completed by participant and scanned.
- *Form 33D-Medical History Update (Detail)* is completed by participant and key entered.
- Potential outcome is identified and a current Release of Information is obtained.
- Medical records documentation is requested, received, and key entered.
- Adjudication case packet is assembled and local adjudication is pending.

The participant's pending and closed adjudication case packets must be forwarded to the receiving CC for permanent archiving. Photocopy the case (medical record documents, *reports* [Member Outcomes Status Report *WHIP 1215*] and outcomes forms) and send the original documentation to the receiving CC. The originating CC keeps a copy of the case packet for their records or in accordance with local IRB guidelines.

Participant Contact: If the participant is planning to move but does not yet have a new address and phone number, instruct the participant to contact the originating CC as soon as she is settled in her new location. Confirm that the information on the Member Personal Information report [*WHIP 0441*] is correct in case she fails to establish contact and needs to be located through her personal information contacts.

Once a new address and phone number are obtained, provide the participant with the address, phone number, and name of a contact person at the receiving CC and inform her that the receiving CC will contact her. Give her an estimated timeframe as to when she should expect to be contacted by the receiving CC. A DM intervention participant should also be given the name and phone number of the receiving Lead DM Intervention Nutritionist.

The ancillary study PI will determine appropriate ongoing follow-up of ancillary study participants. Thus, for an ancillary study participant who is transferring to a CC that is NOT involved in the ancillary study, contact the ancillary study PI for specific transfer guidelines and discuss with the participant her ongoing participation in that study before completing the transfer.

Participant Files: Make copies of the participant file and send the original or copy to the receiving CC. Include any information, such as DM intervention notes, HRT notes or outcomes documents, that may be kept in separate files (DM Intervention notes may be sent in an appropriately marked separate envelope). To decrease the burden of copying and archiving the entire participant file, the originating CC may copy only the information required for archiving at their CC in accordance with local IRB and state laws. You do not need to copy or send the CC's internal tracking forms. Review the files for accuracy and completeness before sending them to ensure the transfer process goes smoothly.

17.5.2 Transfer Team Procedures (Receiving CC)

The receiving CC CM and/or transfer team will review the participant and her proposed transfer. During this review, complete the following tasks:

- Fill out and sign Part II of *Form 22 – Participant Transfer*.
- Discuss information currently available from the originating CC. Appropriate receiving lead staff should talk with appropriate originating staff (e.g., the receiving Lead Nutritionist should contact the originating Lead Nutritionist for DM intervention participants).
- Identify an appropriate receiving CC staff person (e.g., LN) to conduct a phone interview with the participant to establish continuing interest in study participation. This interview should take place as soon as it is feasible after the originating CC's initial contact. Include a discussion of such issues as travel distance and contact schedules. If a receiving CC cannot provide services that the originating CC has been providing (such as transportation, bone density scans, in-house mammograms, or non-English speaking staff), discuss these issues thoroughly with the participant to ensure they will not be barriers to her retention at the receiving CC. Schedule the next routine visit, even if the target date is sometime in the future.

The receiving CC should also establish if it is appropriate to have a CC visit before the transfer is approved and/or before the next scheduled routine contact. Note that a visit to the receiving CC before the potential transfer participant is actually approved may not be practical and is not required. If it is decided to conduct a clinic visit before the transfer is completed, make sure you are aware of your local IRB guidelines for conducting a clinic visit with a participant without a signed consent. It is important that the receiving CC has sufficient contact with the participant by phone and/or mail to establish rapport and determine her interest in continuing in the study at the new CC. If a participant does not want to attend visits there, the originating CC can continue follow-up by mail and/or phone and attempt to schedule visits. However, you may need to "stop intervention" (on *Form 7 – Participation Status*) for those participants who cannot be seen at their assigned CC. Guidelines for determining minimum requirements for staying on "active intervention" are in *Vol. 2, Sect. 16.4.2 – Minimum Procedures Required For A CT Participant To Remain On Intervention* (Required) and *Vol. 2, Sect. 17.2.1 – Identifying Retention Challenges and Tracking Special Activities.*

Participant Contacts Before Transfer Procedures Initiated: If a participant contacts a receiving CC that has not yet been contacted by the originating CC to initiate a transfer, be cautious how you respond to the participant. Instead of telling the participant that you are not aware of her transfer (and can't help her), consider taking the following steps:

- Explain to the participant that information needs to be obtained from the originating CC.
- Obtain her address, phone number, and other contact information.
- Let her know who will be contacting her again.
- Contact the CM at the originating CC for more information and/or to formally initiate the transfer process (it is possible that the originating CC doesn't know that the participant has moved).

Nutrition: A DM Intervention participant retains the diet goals (fat, fruit/vegetable, grain) assigned at the originating CC. Attendance and performance data from sessions completed at the originating CC are also retained, except in the following situations:

- if the participant is assigned to an intervention group at the receiving CC before that group completes the sessions already completed by the participant at the originating CC, and
- if the participant repeats the session(s) at the receiving CC.

For both exceptions, data collected at the receiving CC become the participant's data. To avoid a break in the dietary intervention, DM intervention participants should be assigned to an active intervention group and resume session attendance as soon as possible after the transfer.

It is highly recommended that the LN or other designated nutrition staff person at the receiving CC make the initial contact with the DM Intervention participants.

HRT/CaD: The receiving CP (HRT, CaD) or appropriate other staff person (CaD) should complete the following tasks:

- Discuss participant's current status with the originating CP.
- Review information from the originating CC.
- Contact and welcome the participant soon after her arrival.
- Schedule her next appointment.
- Determine whether there are any problems, questions, or a need for more study pills.
- Continue any IAP activity that was initiated by the originating CC.

17.5.3 Procedures to Finalize Transfer (Originating/Receiving CC)

Each CC needs to approve the transfer and sign off on *Form 22 – Participant Transfer* before the participant can officially transfer (i.e., in WHILMA). Participants will need to sign a CT or OS consent (as appropriate) for the receiving CC at the first visit or before data is collected. It is recommended that participants signed HRT Update(s) sent from the originating CC be filed with the new HRT consent form the participant signs at the receiving CC.

Refusal of Transfer Participant: A receiving CC may refuse to accept a transfer for any one of the following three reasons:

- The participant refuses to attend clinic visits at the receiving CC.
- The receiving CC is unable to accommodate non-English speaking participants (assessed on a case by case basis by the receiving CC).
- The participant is an OS participant and has already completed AV3.
- The receiving CC has the option to accept an OS participant after AV3 has been completed if they choose to do so.

Issues that cannot be resolved on the clinic management level can be discussed between the respective PIs.

17.5.4 CCC Transfer Procedures

Send only the last page (page 3) of *Form 22 – Participant Transfer* to the CCC. The CCC will return the *Form 22 – Participant Transfer* to the originating CC if the last page of the form (page 3) is not complete. Once the CCC receives a completed *Form 22 - Participant Transfer* (page 3 only) from the receiving CC, the transfer will be considered to be approved, regardless of whether the participant ever visits the receiving CC. All WHILMA records for the participant will be removed from the originating CC's database and copied onto the receiving CC's database. Allow a minimum of one week from the time the CCC receives page 3 of *Form 22* for the WHILMA database records to be transferred from the originating CC to the receiving CC.

The CCC will notify both the originating and receiving CCs of the transfer when it is complete. Transferred participants will retain their original eight-digit member ID number (2-digit CC ID, 5-digit member suffix and check digit) following a transfer. The originating CC will retain credit for the randomization for any participants transferred after randomization.

Once the actual transfer of WHILMA data is completed, the receiving CC is responsible for follow-up and tracking of the participant. For DM intervention participants, the intervention group assigned at the originating CC will appear in the receiving CC's record of intervention groups, but only the data for that transferred participant's activity in that group will be transferred.

If any of the transfer participant's *Form 33s – Medical History Updates* have been analyzed in the WHILMA outcomes analyzer at the originating CC, the analyzer batch(es) from the originating CC with only the transfer participant's form(s) in it will be transferred to the receiving CC's database.

17.5.5 Ancillary Study Transfers

When a participant is transferred from one CC to another, all of her forms and other WHI data are moved to the receiving CC's database. However, her ancillary study enrollments are not transferred along with the rest of her WHILMA data. This is because only a subset of CCs participate in any given ancillary study. Thus, it is especially important that the originating CC and the receiving CC communicate about ancillary studies when initiating a transfer. If the receiving CC is not participating in the ancillary study, then no action is needed as far as WHILMA is concerned. If a participant is enrolled in an ancillary study and is being transferred to a CC that is also participating in that ancillary study, the receiving CC will need to enter the ancillary study enrollment into its database once the other WHILMA records are transferred. Please contact your CCC Data

Coordinator liaison for assistance with this. Originating CCs should remember to send ancillary study consents or data forms to the receiving CC along with the rest of the participant chart if the ancillary study is one in which the receiving CC is participating. You may also need to inform the ancillary study coordinating center of the transfer. Include the information on *Form 22 – Participant Transfer*.

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17.6 Participants Who Move To Area Without Local CC

If a participant has moved to an area without a local CC, she may still be able to continue to participate, if willing.

DM Participants - Because there are no required annual safety procedures for DM participants, it is possible for them to remain on full intervention participation status without coming to the CC for annual visits. However, their follow-up status would need to be changed to "partial follow-up", since they would be unable to come in for clinic visits. For these participants, every effort should be made to collect follow-up data by phone or mail for the duration of the study.

HRT Participants - Participants on HRT may remain on full intervention if they are willing to complete the required safety procedures outlined in *Section 16.4.2 - Minimum Procedures Required for a CT Participant to Remain in Intervention*. For those who are unwilling or unable to complete the required procedures, indicate "Stop HRT Intervention" on *Form 7 - Participation Status* and retrieve study medications (see *Section 16.4.2 - Minimum Procedures Required for a CT Participant to Remain in Intervention*). These participants, if willing, should remain on "partial follow-up" and every effort should be made to collect follow-up data by phone or mail for the duration of the study.

CaD Participants - Participants on CaD may remain on full intervention if they are willing to complete the required safety procedures outlined in *Section 16.4.2 - Minimum Procedures Required for a CT Participant to Remain in Intervention*. For those who are unwilling or unable to complete the required procedures, indicate "Stop CaD Intervention" on *Form 7 - Participation Status* and retrieve study medications (see *Section 17.4.4 - Retrieving Study Pills [HRT and CaD]*). These participants, if willing, should remain on "partial follow-up" and every effort should be made to collect follow-up data by phone or mail for the duration of the study.

OS Participants - OS Participants may remain on full follow-up if they have already completed their 3-year clinic visit and are not at a bone density site. Follow-up data collection (by mail and phone) will proceed as usual for these women. For those who have not completed all of the necessary clinic visits, change their follow-up status to "partial follow-up" and attempt to collect follow-up data by mail or phone for the duration of the study.

For all participants who move outside of the area, be sure to update and data enter *Form 20 - Personal Information.*

Figure17.1
Sample Form to Track Contact Attempts

1. Phone calls to the participant:

Phone Number	Date	Home or Work?	Time of Day	Outcome

2. Mailings to participant:

Date of Mailing	Details (what was mailed)?	Outcome

3. Phone calls to personal contacts

Name of first contact: _____

Phone Number	Date	Time of Day	Outcome

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Figure 17.1 (continued)

Phone calls to personal contacts

Name of second contact: _____

Phone Number	Date	Time of Day	Outcome

4. Phone calls to participant's personal health care provider:

Name of health care provider: _____

Phone Number	Date	Time of Day	Outcome

Figure 17.2
Intensive Adherence Program Checklist

- Affix label here-

Clinical Center/ID: __ __ __ __ - ___ ___ ___ - ___

First Name _____M.I._____

Last Name _____

1. Date IAP initiated: _____
2. IAP Coordinator: _____
3. Reason for enrollment: ___ Low adherence (____% adherence)
   ___ Staff referral

   Adherence problem (short description): _____

4. Steps of IAP:

   4.1 Nature of adherence problem (historical, current timing, cues, etc.)

   4.2 Self Monitoring: If Daily Diary assigned, date of recheck: _____

   4.3 Identify problem antecedents and reinforcers (symptoms, emotions, cognitions, behaviors, and/or difficult situations)

   4.4 Identify solutions

   4.5 Reinforce appropriate attributions

   4.6 Check for success

5. Date IAP ended: _____
6. Plan: _____

   ___ Return to routine follow-up
   ___ Refer to Retention Specialist for further evaluation
   ___ Re-evaluate in 6 months
   ___ Other: _____

Figure 17.3
IAP Participant Call Record

ATTEMPTS						
	Day	**Date (MM-DD-YY)**	**Time (HR:MIN)**	**Spoke With**	**Comments**	**Date of Next Call**
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						

Figure 17.4
Daily Adherence Diary

Name: _____

Study: HRT CaD

Begin monitoring on:

Day/Date: _____

Day/Date	Took Pills?		Any unusual events today?	Any symptoms today?
	HRT _____ # of pills	CaD _____ # of pills		

Figure 17.5

Transfer Checklist*

(not data entered)

Instructions: This Transfer Checklist is an optional form to be used by both the originating and receiving CCs. Part I is completed by the originating CC and Part II by the receiving CC. Information on this form can be revised as often as necessary to communicate pertinent information between the originating and receiving CCs.

Part I Originating CC

Participant Name: _____ ID Number or ID Label: _ _/ _ _ _ _ _/ _

Date of participant's move: ___/___/___

Check all that apply:

❑ DM ❑ HRT ❑ OS ❑ CaD

❑ Subsample ❑ WHIMS ❑ Ancillary study: _____

Form 22—Participant Transfer Circulation:

	❑ CM	❑ CP	❑ OCS
	❑ LN	❑ DC	❑ Other
Exit interview conducted	❑ Yes	❑ No	___/___/___
Other: _____	❑ Yes	❑ No	___/___/___

Notes: _____

_____

Sent to receiving CC:

	Fax	Mail	Date Sent	Staff ID
Contact schedule (*WHIP 0472*)	❑	❑	___/___/___	___ ___ ___
Contact notes	❑	❑	___/___/___	___ ___ ___
Form 22 – Participant Transfer	❑	❑	___/___/___	___ ___ ___
Reports				
WHIP 0618- Tasks Missed at Visit	❑	❑	___/___/___	___ ___ ___
WHIP 1215-Outcomes Status	❑	❑	___/___/___	___ ___ ___
WHIP 1260-Pill Adherence	❑	❑	___/___/___	___ ___ ___
WHIP 0428-Individual Progress	❑	❑	___/___/___	___ ___ ___
WHIP 0441-Personal Information	❑	❑	___/___/___	___ ___ ___

Notes: _____

_____

*For CC use only. Do not send checklist to CCC.

Part II Receiving CC

Form 22—Participant Transfer Circulation:

❑ CM ❑ CP ❑ OCS

❑ LN ❑ DC ❑ Other

Participant Contact: ___/___/___ Staff ID: ___ ___ ___

❑ Yes ❑ No Willing to attend clinic visits

❑ Yes ❑ No Explained transfer process

❑ Yes ❑ No Appointment scheduled ___/___/___

❑ Yes ❑ No Sent welcome letter ___/___/___

❑ Yes ❑ No Concerns identified:

- ❑ Transportation
- ❑ Adherence
- ❑ Retention
- ❑ Other: Specify _____

❑ Form 22 signed by both CCs and sent to CCC on: ___/___/___ Staff ID: ___ ___ ___

Notes: _____

_____

Follow-up needed (include staff ID number and date):

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Table 17.1
Summary of Retention Activities

Ongoing Retention Activities - All Participants (Refer to Vol. 2, Sections 2, 3, 4, 16, 17, and 20 for details)
CC Environment and Facilities (Sections 2, 17) • Make pleasant and appealing to participants • Provide convenient transportation and parking • Reimburse for travel expenses and parking, if necessary • Recruit volunteers to drive participants, if necessary • Post easy to follow signs and directions • Provide easy telephone access • Offer convenient clinic hours • Add weekend and evening hours, if necessary • Provide private area for interviews • Display health information materials in waiting area
Participant/Staff Relations (Sections 2, 17) • Maintain professional appearance • Use CC staff who have good interviewing skills • Make sure interactions are always pleasant and reassuring • Give clear and consistent instructions • Encourage active listening and open-ended questions to foster discussion • Enlist the help of a participant ombudsperson and/or advisory group
Tracking (Sections 4, 16, 17) • Use WHILMA tracking system • Send appointment reminders (include reminder phone calls 24-48 hours before appointment) • Follow-up on no-shows
Involvement of Family Members (Sections 2, 17, 20) • Invite family members to visits and special events • Encourage learning about study's purpose and design • Encourage proxy contact if participant dies or becomes ill
Participant Materials (Sections 3, 17) • Include logo and catch-phrase on recruitment and retention materials • Use at least 12-point font and sufficient white space • Make materials attractive and appealing • Make materials clear, consistent, and understandable • Prepare written materials at a 6th grade reading level • Spell and grammar check materials
During Screening (Sections 4, 17) • Effectively screen out of women who seem unlikely to stay in the trial (e.g., history of mental illness, substance abuse; negative attitudes about the study; non-compliant; confused by information; low literacy; transportation problems) • Send reminder letters for clinic visits • Conduct thorough informed consent discussions
During Enrollment/Randomization (Sections 4, 17) • Provide baseline welcome packet with folder, magnet, member ID card, "Welcome to" handouts, calcium handout, chart stickers, exercise brochure, other health education materials, appointment reminders, other component-specific information, CC contact information

Table 17.1 (continued)

Clinic Visits (Screening or Follow-up) (Sections 4, 16, 17) • Send "Thank you" cards within a week of CC visits • Keep waiting and appointment times to a minimum • Conduct exit interviews to debrief and prepare for next contact • Have consistent contact person to ensure continuity during visit • Provide clear, easy-to-follow instructions for completing activities • Ensure materials are informative about the next contact/visit • Provide phone number and contact name in case participant has questions • Provide incentives, if available • Transfer participant if she moves to another area with a CC
Older Participants (Sections 2, 17, 20) • Keep magnifying glass or reading glasses in form-completion area • Use large font-size in materials
Retention Incentives (Section 17) • Provide annual follow-up visit and other incentives • Send Birthday, thank you, anniversary, bereavement, holiday cards • Annual participant newsletter mailed by CCC
Follow-up Contacts (Sections 16, 17) • See "Clinic Visits" above for follow-up visits • Contact participants who are difficult to reach at several different times and days • Encourage some participation, even if participant is unwilling to stay on intervention or come in for visits • Initiate special retention activities for participants who are difficult to schedule for contacts • Ensure that minimum safety procedures are completed at follow-up contacts for participants on HRT and/or CaD intervention • Mail out a friendly postcard annually to participants who have requested "no follow-up" (but not to those who have requested "absolutely no follow-up") • Try to get participants who miss follow-up contacts back on schedule as soon as possible • Missed annual visits should be conducted even if the next scheduled contact is a semi-annual contact • Missed 1, 3, 6, and 9 should be conducted even if the next scheduled contact is a semi-annual contact or other annual visit • Missed OS third-year visit can be conducted for up to one year after the third-year target date • To discourage missed contacts/visits, send reminder cards and/or conduct reminder phone calls, or send second mailings to participants who do not respond
Maintaining Up-To-Date Addresses (Sections 16, 17) • Maintain mailable addresses in WHILMA (*run WHIP 0611: Members with an Incomplete or Long Name/Address* monthly and correct any problems) • Maintain complete and deliverable addresses (run *WHIP 1211 - Undeliverable Address Report*) on an ongoing basis • Fix problem addresses as soon as possible; call participant or post office if necessary • Set "undeliverable address flag", if necessary • Contact CCC immediately if CC return address listed on newsletter changes

Table 17.1 (continued)

Searching for Lost Participants (Section 17) • Initiate search for lost participants using *Form 23 - Search to Locate Participant* and data enter • Conduct appropriate activities as necessary: -attempt to reach by phone -attempt to reach by mail -contact personal contacts -contact physician -contact other sources • Continue to repeat attempts over a 6 month period if early attempts are unsuccessful • Update WHILMA with any new contact information (e.g., new address) • When search is completed, indicate search result on *Form 23 - Search to Locate Participant* and data enter • Complete *Form 7 – Participation Status* if appropriate • Periodically re-open search for "lost to follow-up" participants
Procedures for Conducting Special Activities for Retention Challenges (Section 17) • Conduct all activities necessary and appropriate to situation and study component -see component-specific strategies summarized in tables below -refer to appropriate sections of Volume 2 for component-specific strategies: *Sections 5 (HRT), 6 (DM), 7 (CaD), 8 (OS), 15 (Medications), 16 (Follow-up Contacts), 17 (Retention)* • Track activities by completing *Form 24 – Adherence and Retention Worksheet* • Complete *Form 7 – Participation Status* if appropriate
Participation Status (Sections 16, 17) • Initiate retention activities, if appropriate, before changing status • Conduct search for participant, if appropriate, before changing status • Complete *Form 7 – Participation Status* if participant's intervention or follow-up status change • Periodically contact "no follow-up" and "no intervention" participants, as appropriate, to see if they are willing to change status

Table 17.1 (continued)

Summary of Specific Retention Activities - DM Participants (Refer to Vol. 2, Sections 4, 6, 16, and 17 for details)
CC Environment and Facilities (Sections 6, 17) • Use comfortable classroom for DM Intervention sessions
Participant/Staff Relations (Sections 6, 17) • Have investigators present study updates at DM Intervention potlucks • Have Nutritionists call DM Intervention participants when they miss sessions
Tracking/ (Sections 6, 17) • Send reminders (e.g., postcards or letters) to attend DM Intervention sessions and follow-up visits • Use WHILMA reports to monitor DM Intervention participation and progress • Provide reminders for off-schedule mammograms
Involvement of Family Members (Sections 6, 17) • Invite family of DM Intervention participants to DM Intervention potlucks and some session activities
Participant Materials (Sections 6, 17) • Provide DM Intervention participants with session materials and binders • Provide DM Intervention participants with calculators
During Screening (Sections 4, 6) • Use DM Eligibility Checklist • Provide DM participants with measuring cups and spoons, as needed
During Randomization (Sections 4, 6) • Make sure that DM Control participants understand that they are in the study • Provide DM Control participants with USDA brochure of Dietary Guidelines for Americans • Provide DM Intervention participants with "Your New Eating Style" booklet 4 weeks after randomization if they have not yet started group sessions • Have Nutritionists contact DM Intervention participants monthly while they are waiting to start group sessions
Retention Incentives (Sections 6, 17) • Provide/send DM Intervention newsletter to DM Intervention participants, Year 2+ (Maintenance years) • CC retention activities for DM Control participants are allowed, but not required
Activities for Retention Challenges (Sections 6, 17) • Have Nutritionists contact DM Intervention participants after they miss sessions to schedule make-up sessions • Use high intensity Intensive Intervention Protocol (IIP) procedures for Level 2 and Level 3 participants having difficulty meeting Dietary Change goals • Use low intensity Interrupted DM Intervention Participation procedures for Level 4 participants having difficulty completing Dietary Change sessions

Table 17.1 (continued)

Summary of Specific Retention Activities - HRT and CaD Participants (Refer to Vol. 2, Sections 4, 5, 7, 15, 16, and 17 for details)
CC Environment and Facilities (Sections 4, 17) • Have BSE audiovisuals available • Don't have articles promoting/discouraging HRT or CaD use in waiting area • Make sure GYN exam room is clean, well-lit, secure, "friendly"
Participant/Staff Relations (Sections 15, 17) • Provide participant with a contact phone number to call if she has questions or concerns • Ensure that a clinician is available to respond to participant questions and concerns • Promote bonding by having all HRT contacts with the same knowledgeable staff members
Tracking (Sections 16, 17) • Provide reminders for off-schedule mammograms • Use reports and a tickler system for routine and non-routine calls/visits
Involvement of Family Members (Section 17) • Provide explanations and incorporate support for pill-taking
Participant Materials (Section 17) • Keep participant up-to-date on science of HRT • Develop materials that explain what recent studies about HRT really mean, in lay language
Before Randomization (Sections 4, 5, 7, 15) • Treat enrollment pills as regular study pills • Stress need for adherence and retention • Assess potential for bleeding (e.g., pre or perimenopausal) and its impact on participant's willingness to stay on HRT intervention • Ensure participant is willing to be randomized to active or placebo study pills • Clarify possibility of side-effects and stress availability of methods to deal with them
Follow-up Contacts (Sections 5, 7, 16) • Maintain schedules to ensure safety • Offer HRT Handbook and/or CaD Instruction Sheet at each contact • Offer pill organizer at each contact • Premedicate and/or use local anesthesia for participants who undergo endometrial aspirations
Identifying Retention Challenges (Sections 5, 7, 15, 17) • Complete *Form 10* and/or *17* at each participant contact and assess indicators of adherence • Discuss difficulties with adherence with participants during visits
Activities for Retention Challenges (Sections 5, 7, 15, 17) • Ensure participant has pill organizer, HRT Handbook, or any other relevant materials • Provide participant with cues for pill taking (e.g., at bedtime, when you get up, with meals) • Emphasize importance of answering the study's scientific questions and how no one can take her place • Offer to discuss concerns with participant's personal physician • Initiate the Intensive Adherence Program for those with <80% adherence
Changing Participation Status (Sections 5, 7, 15, 16, 17) • Offer participant self-management and/or step-down of study pills, rather than immediately discontinuing pills for symptoms (e.g., breast tenderness, bloating, hot flashes, GI discomfort) • Utilize algorithms and alternative dosages to decrease side effects • Stop intervention if participant is not meeting safety requirements • Retrieve study pills if intervention is stopped • If participant is willing, re-initiate study pills in women who have previously stopped, even at a minimal level

Table 17.1 (continued)

Specific Retention Activities - OS Participants (Refer to Vol. 2, Sections 4, 8, 16, and 17 for details)
Tracking (Section 16) • Indicate returned packets by either: scanning barcode in receipt screen or key-entering returned forms • Run *WHIP 1207 - Returned Packet with Missing Form* monthly to identify packets with missing Form 33 needing follow-up or track for data entry
Maintaining Up-To-Date Addresses (Sections 16, 17) • Maintain addresses in WHILMA (*run WHIP 0611: Members with an Incomplete or Long Name/Address* monthly and correct problems) • Update WHILMA if Post Office notifies of address change following non-delivery of OS mailing • Maintain complete and deliverable addresses (run *WHIP 1211 - Undeliverable Address Report*) on an ongoing basis • Fix problem addresses identified by *WHIP 1211* as soon as possible; call participant or post office if necessary • Set "undeliverable address flag" if necessary • Initiate search for lost participants using *Form 23 - Search to Locate Participant*
Materials (Section 16) • Contact CCC immediately if CC return address on OS mailing envelopes used by the CCC needs to be changed
During Enrollment (Sections 4, 8) • Make sure OS participants understand that they are in the study
Follow-up of Non-Respondents (Sections 16, 17) • Run *WHIP 1206 - OS Enrolled Members Needing CC Follow-Up* monthly for list of non-respondents requiring CC telephone data collection • Make telephone contact to ascertain correct address and collect *Form 33 - Medical History Update* • Update address in WHILMA, as appropriate • Collect data from proxy, if participant is deceased, unable to communicate, has poor cognitive functioning • Complete *Form 7 - Participant Status* if participant, as appropriate (e.g., if participant is deceased)

Table 17.2
Summary of Clinical Center Activities for Retention Challenges

		Retention Challenges	Identifying Retention Challenges	Special Activities for Retention Challenges	Documenting Special Activities	Tracking Special Activities	Ending Special Activities
Intervention	**HRT/CaD**	Low or non-adherence to pill taking regimen	• Pill count • Ppt self-reports low adherence • Ppt comments indicate low adherence • Ppt refuses pills *HRT/CaD Medication Adherence* (*WHIP 1260*) *CaD Management Recontact* (*WHIP 1048*)	IAP (Section 17.2.2.2.1)	• *Form 10 – HRT Management and Safety* • *Form 17 – CaD Management and Safety* • *Figure 17.2 – IAP Checklist* • *Figure 17.3 – IAP Participant Call Record* • *Form 24 – Adherence and Retention Worksheet* • Clinical Contact Notes	*Member Adherence and Retention Activity Tracking* (*WHIP 1238*)	• Adherence improves. • Adherence doesn't improve, but all special activities have failed. • Participant refuses study pills, and all special activities have failed.
	DM	Not meeting Dietary Change goals (Level 2 + Level 3)	*IIP Triage & Tracking (WHIP 0444)* *Individual Progress* (*WHIP 0428*)	Intensive Intervention Protocol (IIP) (Section 6.11)	• *Form 64 – Individual Data Sheet* • GN Progress Notes	*IIP Triage & Tracking (WHIP 0444)*	Participant refuses contact with nutrition staff, and all special activities have failed.
		Not completing Dietary Change sessions (Level 4)	*IIP Triage & Tracking (WHIP 0444)*	Interrupted DM Intervention Participation (Section 6.10.8)	• *Form 24 – Adherence and Retention Worksheet* • GN Progress Notes • *Figure 6.3 – Interrupted DM Intervention Worksheet*	*IIP Triage & Tracking (WHIP 0444)* *Member Adherence and Retention Activity Tracking* (*WHIP 1238*)	Participant refuses contact with nutrition staff, and all special activities have failed.
Follow-up	**CT and OS**	Not attending follow-up visits Not accepting f/u phone calls/mail	*Missed Scheduled Visit (WHIP 0799)* *OS Enrolled Members Needing OS Follow-up (WHIP 1206)*	16.4 16.5 16.6 16.7	*Form 24 – Adherence and Retention Worksheet*	*Member Adherence and Retention Activity Tracking* (*WHIP 1238*)	Participant refuses all follow-up participation (including safety procedures for HRT and CaD), and all special activities have failed.

Table 17.3
Reasons for Poor Retention and/or Adherence

Interactions between participants and study staff are critical to maintaining or regaining retention and/or adherence and performance. During these interactions, staff may discover the participant's reasons for wanting to change her participation status, or for low adherence to the intervention. Learning the reasons for wanting the change may help you determine your strategy to help keep the participant in the study. Some common reasons are:	
Lack of Knowledge	The participants may not have the knowledge necessary to fully participate. Participants forget instructions and may not remember what to do if something goes differently from the standard procedures. Participants may also change their behavior based on incorrect knowledge. Never assume that the participant understands and knows what to do without some form of check and review of the activities necessary to follow the regimen.
Lack of Long-Term Cues	The participant may drift off the intervention due to boredom, lack of reminders, or no recall as to why she joined in the first place.
Lack of Skills	The participant may not have the necessary skills to carry out the intervention procedures. For example, memory skills are critical to good adherence and retention. Participants may not know how to set up a personalized reminder system to cue activities, for example, to help remember to take their study pills. Discussing and even practicing the steps of a reminder system may help some participants. Assertiveness skills may be necessary for some activities. Participants need to feel comfortable calling the CC to ask questions, to report problems, or to reassure themselves that they are not harmed by the intervention. Make it clear that calling is appropriate and not a burden.
Conflicting Beliefs About the Intervention	The participant may hold a set of beliefs or ideas that are different from either the standard medical knowledge or from the study staff. Examples of these beliefs include the idea that the CC staff is not helpful or honest, that the participant is on an incorrect or inappropriate intervention, that she has received contradictory advice from friends, that she has incorrectly attributed symptoms or health problems to the intervention, or the she misunderstands what the intervention was supposed to do for her (e.g., lose weight, feel better, etc.).
Fear of Negative Health Consequences Due to Participation	The participant may hold beliefs and feelings about the intervention that interfere with adherence and/or retention. The most common of these is fear, including fear of the meaning of current symptoms, fear of future health problems, and fear of other negative consequences of study activities or procedures. Participants may worry that the intervention (or lack of intervention, if they are in the control group) will have a negative impact on their health.
Adverse Physical Reactions or Symptoms Resulting from the Intervention	Some women will experience symptoms as a result of the intervention, especially those women in the HRT or CaD components. These symptoms may make a participant so uncomfortable that she is unwilling to continue her participation in the intervention. Participants in the DM dietary change component may also incorrectly attribute health symptoms to be a result of changes in their diet.
General Health Issues	A participant's health may deteriorate over the course of the study, which may change her priorities.
Environmental Issues	The participant's environment may not be supportive of or may actively discourage full participation. Changes in home and family priorities, lack of time, logistical difficulties, unemployment, financial needs, stress, and other life changes may interfere with adherence and retention. There may be a lack of support from family or CC staff or a feeling that their participation doesn't contribute to science or the good of others. For example, the participant may inform her spouse of symptoms and the spouse may respond, "That hormone study is no good for you."
Life Events	Often life events may occur that can get the participant off the track and she may forget to get back into the intervention. These types of events tend to be more episodic than environmental issues.

Table 17.4
Strategies to Retain Full Participation in CT and OS

There are several activities that CC staff can use when encouraging participants to fully participate in the component to which they have been assigned. You may use these activities during regularly scheduled follow-up contacts, or with participants who are expressing reluctance to continue to fully participate or who are having adherence problems. You may need to make special attempts, either by mail, phone, or both, to contact those participants who have not shown up for regular intervention and/or follow-up activities.

Reinforce the Importance of WHI and Remind Participants of Their Original Commitment to WHI

- Reinforce the contributions made to-date and thank the participant for her participation.
- Remind her that her contribution is valuable and that every person's information will be necessary to reach the goals of WHI.
- Revisit the larger scientific goals and the exciting potential of WHI to answer critical questions about the health of women of all ages.
- Remind her of the contribution she is making to future generations of women.

Identify and Update Participants' Competing Beliefs and Motives

Participants join and maintain their activity in studies like the WHI for a variety of reasons. They also hold beliefs about the study and procedures that may or may not fit with current medical knowledge. These beliefs may have come from well-meaning family or friends and may not be accurate. In the face of ambiguous information in the press (for example, about HRT), participants may develop certain beliefs to explain sensations or observations about the effects of the intervention.

- Talk with the participant to uncover her beliefs about the study that may be causing her to limit or stop her participation. Discuss these beliefs without discounting what the participant is saying.
- Tell her about new studies that contradict these beliefs. Explain how she could have come to conclusions based on the evidence and show her how alternative explanations for what she has observed can also be true.
- Try to chip away at these beliefs using existing evidence to remove barriers to adherence.
- Ask the participant to discuss the problem with her primary care provider, since her problems might be due to other health problems.
- Consider having the Principal Investigator contact the participant's primary care provider to discuss the issue.

Identify Participant's Fears and Concerns

Participants may have fears or worries about the study that they do not volunteer at first.

- Probe to find these fears and discuss the reasons for them. Reassure participants when possible, especially if there is medical evidence to refute the fear.
- Do not brush away fears and concerns. Instead, explain how current medical knowledge has uncovered information she will want to consider when making her decision. For example, if a participant mentions her fear of breast cancer while taking hormones, discuss the fact that information from other studies suggest that the benefits of preventing heart disease and osteoporosis may outweigh any increase in risk of breast cancer for most women and remind her that we will monitor her throughout the study to help ensure her safety.

Anticipate and Reduce Negative Effects of Participation

One of the predictors of adherence and retention problems is the negative events (e.g., symptoms) that come from participation. These include symptoms that are caused by the study pill preparation, interference of the intervention with other activities, social barriers, etc.

- Discuss all barriers, whether experienced or anticipated, with the participant.
- Participants may need reassurance that symptoms are a normal part of getting used to the intervention (e.g., study pills).
- Interference and social difficulties resulting from participation should be addressed immediately. Probe for these at all visits. For example, participating in DM intervention may cause problems in family and social situations for dietary change participants. Try to help the participant find methods of reducing these difficulties.

Identify Problems with Convenience and Accessibility

Often participants will not stay with the study due to the inconvenience of visits or inaccessibility of the CC. If these are a problem, try to work with the participant to arrange a schedule of visits that fits with her schedule. Try to make transportation arrangements for the participant, if possible. If she is unable to attend CC visits on a regular basis, try to conduct as much of the follow-up as possible by telephone and mail.

Identify Sources of Social and Emotional Support for Participant

The relationship between the Clinic Practitioner (CP) and other clinic staff (e.g., the group nutritionist for DM dietary change participants) and the participant can be a source of social and emotional support for participation. Indicate at every reasonable opportunity that you appreciate the participant's efforts, that you are there to help her, and that you know that she can succeed in her study participation. The latter is critical, because she will likely interpret any silence on the CP's part as evidence of lack of confidence. Ask her if she has any other sources of support and encourage her to use these in addition to using CC staff.

Negotiate Any Level of Activity Possible Within the Confines of the Protocol

If you have exhausted retention activities and the participant still wants less than full participation in the study, try to keep her involved in study activities to the extent possible. Some activity is better than no activity. For example, a participant may be willing to complete forms by mail, but unwilling to come in for clinic visits or take phone calls. It is much better to collect data by mail than to not collect any data at all.

Always Leave the Conversation Open to Future Contact

If you are unable to convince the participant to continue as a full participant, keep open the possibility of future contact. Say "I'll be calling you every so often to see how you are doing", if appropriate. Never close the door to a future contact opportunity. Encourage the participant to take a break from the study and that you'll get back to her at a later time. Try to find ways to maintain period contact with participants: send postcards or call her occasionally to let her know you're interested.

Table 17.5
Strategies for Adherence to CT Intervention

Involve the Participant in Improving Her Adherence	The participant must be involved in decisions about strategies to improve adherence. The participant will be more likely to use a strategy for improving adherence if she identifies it herself, rather than receiving it from the CC staff. Ask the participant, "How can you overcome this problem?" rather than, "Here is what you should do to overcome this problem."
Be Concrete and Specific About Steps to Improve Adherence	Be very specific about the steps needed to change behavior when deciding with the participant on a course of action to improve adherence to the intervention. Set a concrete behavioral goal (e.g., "I will put this sign up on my bathroom mirror to remind myself to take my HRT study pills"), then review with her the steps needed to achieve the goal. For this example, the steps could include making the sign, deciding on its placement, discussing it with other bathroom users, hanging the sign in the bathroom, and checking in at the next clinic contact about how the sign is working.
Test to Make Sure That the Communication Exchange Has Been Clear	After every discussion, no matter what the topic, ask if the participant has any questions and give her a few moments to think about it. If there are no questions, ask her open-ended questions to review the topics discussed and the decisions made. Go beyond a simple review of the facts and statements. Attempt to question the participant as to how the discussion will affect the ways she behaves and feels. Review is particularly important when discussing instructions for conducting specific intervention activities or a new procedure.
Give Direct Skill Training and Rehearsal When Necessary	When you identify new activities and skills to improve adherence, practice them with the participant to ensure clarity and her comfort in conducting them. For example, if you and the participant have identified assertiveness as a needed skill, practice what the participant will say in the problem setting. If you both have identified a method for reminding her to take her pill every day that involves a change, rehearse it out loud during the visit or telephone call. Talk through the steps one-by-one until both of you are convinced that the participant has a clear vision of what needs to change. Begin by saying, "Let's run through it here in the office so that when you get home it will be easy."
Design Reminder Systems	Designing reminder systems may help the participant adhere to her intervention activities. Discuss with the non-adherent participant the reasons why she seems to be forgetting to follow the intervention and help her design a set of reminders that will help her stick to it (e.g., to take her daily pill). Remember to design the reminder system so that unusual days (e.g., vacations or traveling) are incorporated. Have the participant rehearse the steps to implement and use the reminder system before she leaves the clinic. Refer to other sources for strategies to remember to follow the intervention, for example, HRT participants should refer to the HRT Handbook and DM intervention participants should refer to their study manual.
Use Cognitive Rehearsal Strategies	Have the participant take time in the clinic to visualize herself carrying out the steps to good adherence that you have just discussed with her. The common steps in cognitive rehearsal are 1) Relax for a few minutes, 2) Imagine herself actually performing the activity, and 3) Visualize the success of the strategy or activity. Ask her what it will look like and how it will feel. This is a good method for identifying problems that might come up during the course of the activity.
Provide Support	Reinforce the participant's efforts, no matter how small. Help her to feel needed by indicating that her participation is valued and critical. Listen to her problems and indicate that her concerns are real and important. Reinforce the presence of the CC staff in helping to solve problems related to WHI.

Table 17.6
Examples of Retention Strategies

The following is a list of strategies that CC staff may use in an attempt to keep the participant fully participating. Use any strategies that seem appropriate. None of the activities are required and CC staff are encouraged to design their own activities.

- Initiate contacts with the participant:

  Emphasize the participant's important personal contribution to WHI: Make participant feel important and valuable to the study.

  Describe the scope and significance of WHI: Review the WHI goals and participant's contribution to goals.

  Emphasize the importance of participant: Remind participants of early commitment and consent.

  Remind the participant that WHI is research, not health care: Remind participants to see primary care provider.

  Express appreciation for the participant's effort in the project so far: Thank participant at every opportunity.

  Invite participant to talk with Clinic Practitioner: Schedule the Clinic Practitioner to discuss issues with participant.

  Remind the participant of the careful monitoring for side effects during visits and phone calls: Try to calm any fears about side effects that may result from participation.

  Remind the participant of the careful monitoring for side effects during the visits and phone calls: Try to calm any fears about side effects that may result from participation.

  Invite family or friends to CC with participant for discussion: Discuss problem issues as a group to help participant with social problems.

  Ask participant to discuss study participation with family or friends: Encourage participant to tell others of her commitment to WHI.

  Invite the participant to talk with CC Manager about questions/concerns: Schedule a time for participant to discuss with the Principal Investigator.

  Ask if the participant wants the Principle Investigator to talk with her personal physician: Schedule the Principle Investigator to call the participant's health care provider.

  Discuss fears about consequences of intervention and reassure as appropriate: Probe for fears and discuss reasons for them. Reassure participant when possible, especially if there is medical evidence to refute the fear.

  Probe for and clarify misconceptions about the study: Provide literature, as appropriate. Clarify misconceptions about symptoms, risks, etc.

  Discuss barriers to participation and help find ways to reduce: Brainstorm with the participant to address barriers.

  Anticipate and reduce negative effects of retention/adherence: Probe for negative effects, such as barriers, symptoms, time factors. Help the participant find ways to reduce these difficulties.

- Discuss alternatives to make participation easier:

  Convenient appointment days and times: Discuss alternative visit times or days to make participation easier.

  Annual visits instead of semi-annual: Offer to drop the semi-annual contact, if possible.

  Help with filling out forms during the visit: Provide assistance with WHI procedures, if available.

  Coordinate with other participants: Offer to request carpool participants and to schedule visits with others.

  Help with transportation: Offer compensation for transportation, if available.

Free, safe, or more convenient transportation suggestions: Help participants to identify transportation alternatives.

Security assistance: Offer an escort to the parking lot, if available.

Offer telephone only contact substitution (as last resort): Offer to collect data over the telephone, if possible. No blood draw (as last resort): Offer to reduce or eliminate the blood draw, if possible.

No blood draw (as last resort): Offer to eliminate the Bone Density measure.

Review instructions for required activities: Make sure the participant clearly understands what is expected of her and that she isn't dropping out due to confusion or frustration.

Help design reminders to follow intervention: Work with the participant to design reminder systems (e.g., note on bathroom mirror to help remind to take study pills).

Provide skills training and rehearsal when necessary: Talk with her about the areas she is having problems with and provide skills training, if appropriate.

- Give informational materials/referrals:

Retention incentives: Provide the participant with whatever retention incentives are available at the CC.

Disease prevention literature: The participant may want to stop participating because of misconceptions about the intervention. Provide her with relevant information about the intervention and diseases being studied in WHI, as well as other prevention literature (e.g., quitting smoking), as appropriate.

Disease etiology literature: Provide participant with any available interesting and relevant literature on the causes and prevention of disease.

Tip sheets and other health information: Provide any general health information or information specific to successful WHI participation, as available and appropriate.

Health care referrals: Provide participant with a list of other health care referrals, if appropriate, to help address her health concerns, even those not related to WHI (e.g., referrals for domestic abuse, smoking cessation, etc.).

Physician letter: Provide participant with letters of support from physicians or other health care providers in the community. Or, give her a letter to take to her own physician explaining WHI and have her discuss her participation with him/her, appropriate.

HRT/CaD handouts: Provide participants with any written information about HRT and/or CaD. This the materials provided at any of the screening or randomizations contacts or any other written material, such as brochures, articles, etc.

Review consent form/video: Show the participant the consent video and/or review her consent forms with her if she has questions or concerns about her original consent process. Discuss the issues with her.

New pill dispenser: Provide the participant with a new pill dispenser, if appropriate.

New HRT Handbook: Provide the participant with a new HRT Handbook, if appropriate.

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SECTION 18

DATA MANAGEMENT

INTRODUCTION

Data enter the WHI database (WHILMA) via one of three means: key-entry from a study form, direct entry onto a study screen (without a form), or electronically via scanning of a mark-sense form. Quality of data is assured by a variety of methods including review of completed forms before entry, training of data collection and management staff, participant file audits, and edit checks built into the data entry system. The Clinical Coordinating Center (CCC) also performs routine edits of the central database. Clinical Centers (CCs) must store hard copies of data collection forms in a readily accessible and secure manner, and respond to data queries from the CCC. Carefully recorded, entered, and maintained data are critical to the success of the study.

18.1 Form Flow

Overview

At each participant visit, the following general activities take place:

- CC staff place blank forms that will be used at the particular visit in the participant's file. Sheets of barcode labels with the participant's study ID are generated for use on the forms as needed.
- When the participant arrives, any completed forms that she has brought with her are added to the file. Interviewers and clinicians complete the visit-specific forms inside the file during the visit. They may complete additional forms and add them to the file during the visit. Specimen tracking forms, such as *Form 92 – Pap Smear*, may be removed from the file and temporarily filed elsewhere while results are pending. The CC staff transport the file about the CC; the participant file should not be in the possession of the participant.
- At the end of the visit, the file is sent to the area of the CC set aside for review and data entry activities. Avoid leaving files unsecured or in undesignated areas at the end of the day.
- The data entry staff reviews the file for completeness and accuracy, resolves any forms problems with other CC staff, then scans or enters the data. Most self-administered forms such as *Form 35 – Personal Habits Update* and *Form 38 – Daily Life* are reviewed for completeness only. (See *Section 18.2.3 – Review of Forms* for more detailed information.)
- The file is filed in the file room when data entry is complete.

18.1.1 Specimen Tracking

The following forms are used by the CCs to track specimens that are sent to outside labs for analysis, or to record results of tests that are conducted elsewhere:

- *Form 81 - Pelvic Exam/Pap Smear*
- *Form 82 - Endometrial Aspiration*
- *Form 83 - Transvaginal Uterine Ultrasound*
- *Form 85 - Mammogram*
- *Form 92 – Pap Smear*
- *Form 100 - Blood Collection and Processing*

The *Members with Missing Lab Results (WHIP0782)* (see *Vol. 5 - Data System, Appendix D - WHILMA Reports*) can be used to track specimens or pending tests if the encounter information from the top part of the form is key-entered shortly after the specimen is collected or the test is ordered. The *Members with Missing Blood Results* report can be used to track pending blood results. If desired, CCs can maintain a log of pending specimens or tests that includes the name of the facility doing the analysis or test, the date the specimen is sent or the test result requested, and the date the results are received by the CC.

Incomplete specimen forms can be filed in a central area accessible to CC staff members who will be responsible for completing the forms when results are received. As results are received, clerical staff can match them to the corresponding form and file them according to the staff member(s) responsible for completing the particular form. Clinical Centers can key-enter the forms in a manner that best fits the flow of the CC. Options include:

- Key-enter the entire form after the results have arrived and have been recorded on the form.
- Key-enter the encounter information from the form after the specimen is collected or results requested, then wait for the arrival of the results and key-enter the remainder of the form. This option allows you to use WHILMA to assist with specimen tracking.

After key-entry, both the form and results are filed in the participant's file.

18.1.2 Follow-Up Visits

Before Contact

For each follow-up phone contact or CC visit, CC staff pull the participant's file and add any blank forms that will be needed for the contact. Tasks to be performed at each follow-up contact are shown in the *Tasks Required at Visit (WHIP0144)* report that can be printed from WHILMA for any randomized participant. All forms needed for the follow-up visit are labeled with the participant's barcode and the entire file is given to the CC staff person overseeing the contact.

Day of Contact

On the day of the contact, CC staff members complete the applicable forms and review them before filing them in the participant's file and sending the entire file to Data Entry. Specimen tracking forms and test report forms that are initiated at follow-up visits are handled as described in *Section 18.1.1 - Specimen Tracking*.

18.2 Data Collection (Required)

Study data are collected and entered into WHILMA by certified staff at the CCs, using WHI data collection forms or direct entry screens developed at the CCC. CCs should not develop and use their own study forms without permission from the CCC. Exceptions are visit checklists and forms that are not administered to the participant or used to collect data from the participant.

This section primarily covers the collection, review, editing, and entry of data on study forms. For related topics, refer to *Section 2.11 – Interviewer Procedures* and *Vol. 5 – Data System*.

18.2.1 Data Collection Forms

The U.S. Government Printing Office (GPO) prints most of the WHI forms. To order these forms CCs complete *Form 170 – Forms Order* at scheduled times and submit the orders to the CCC. The CCC consolidates the orders from the CCs and sends a printing request to the GPO. Each CC is responsible for ordering a sufficient supply of forms to last until the next specified printing date. Some forms that are used infrequently are not printed. Instead, the CC will be provided with an original to photocopy as needed. The Table of Contents for *Vol. 3 – Forms* indicates which forms CCs receive from the GPO and which to copy at the CC.

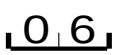
Specific guidelines on completing each individual WHI form are contained in *Vol. 3 - Forms*.

Keep original, completed forms in the participant's file.

Note for ancillary study participants: Forms used only for an ancillary study (not WHI) may be filed in a separate ancillary study chart. For example, *Form 39 – Cognitive Assessment* collected at non-WHI specified times, such as AV4 and AV5, may be filed in a separate chart. *Form 39s* collected at AV3, 6, and 9 should be filed in the participant's WHI chart.

18.2.2 Recording Data on Forms

- Use a pre-printed participant ID label (with barcode) on the front page of each form.
- Complete key-entry forms in black or blue ink. Complete mark-sense forms using a #2 pencil.
- Right-justify numerical data, using preceding zeros if necessary, for example:



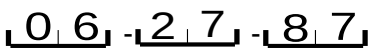
- Use standard rounding rules to round values to the appropriate number of decimal points unless otherwise instructed by the form or *Vol. 3 – Forms*. If a value ends in a fraction less than .5, round down to the next lowest whole number. If a value ends in a fraction equal to or greater than .5, round up to the next highest whole number. Record numbers as fractions ***only*** when there is a decimal point pre-printed on the form.

  If a participant gives a range of numbers in response to a question, and the interviewer is unable to pinpoint a value using interviewing techniques, take the midpoint of the range and use the standard rounding rules to round off as needed.

- Record times as hours 1-12, with a.m. or p.m. indicated in the box provided. Do not use the 24-hour clock. Use leading zeros as necessary. For example, record 2:15 p.m. as:

If exact time of an event is unknown, use the best approximation. If minutes cannot be determined or estimated, record "00" in the space provided for minutes.

- Record dates in MM-DD-YY or MM-DD-YYYY format, where two digits are recorded for month, two for day, and two for year. In some cases, only month and year are requested (MM-YY or MM-YYYY). Add leading zeros as necessary to fill in the boxes:



(See *Section 13 - ECG Procedures* for specific instructions for entering dates into the MACPC.)

- When boxes are provided for recording an answer, clearly mark your choice with an "X." If the instructions indicate to "mark all that apply," mark as many of the responses following as are appropriate.
- Make sure that each item on a form is answered (except those items appropriately skipped in a skip pattern, e.g., "If yes, go to question 4"). If the information is unknown or unavailable, write "unk" next to the question and initial.

18.2.2.1 Recording "Unknown" Responses on Forms

Occasionally a woman will be unable to remember a date or other event that is requested on a form. Responses to questions involving non-date events that affect eligibility (for example, number of meals prepared outside the home) must be provided by the woman in order to determine eligibility. Dates affecting eligibility can be estimated as described below.

Interviewers and other CC staff should use probing techniques (see *Section 2.11.4.1 – Interview Techniques*) to obtain the woman's "best guess" response to questions. When all attempts fail to obtain an eligibility-related date, the estimation procedure described below is used. This method produces a conservative estimate for dates that affect eligibility; therefore it is best if the CC can encourage a woman to provide a reasonable date rather than estimating one.

- For dates that affect a woman's eligibility status:

  If the woman can't remember the year, record the current year.

  If the woman can remember the year, but not the month:

  Record the current month if the recorded year is the current year.

  Record "12" (December) if the recorded year is other than the current year.

  In either case, make a note next to the question indicating that the response is an estimate. Initial and date the note.

- For other "unknown" responses and dates that do not affect a woman's eligibility status:

  Use the above method for estimating the date or leave the response blank. Make a note next to the question on the form to indicate that the answer is an estimate or that the woman was unable to answer the question. Initial and date the note.

18.2.2.2 Recording Data on Mark-Sense Forms

The following guidelines should be used when recording data on mark-sense forms:

- Use a #2 pencil.
- Fill in the bubbles neatly and completely.
- Place the participant's ID label exactly where indicated on the front of the form. The mark-sense scanner cannot read the barcode if the label is crooked.

- Do not staple or punch holes in the *FFQ*. Other mark-sense forms have pre-punched holes. If additional holes are necessary, they should be punched only in the margins of the form.

18.2.3 Review of Forms

Review and edit all completed forms on a daily basis. Interviewers should review and edit forms before giving them to the data entry staff. Review all self-administered forms while the participant is still present in the CC, so that any missing pages can be given to the participant to complete. It is best to review interviewer-administered forms before the participant leaves the CC as well, so that clarifications can be made without waiting until the next visit or trying to reach the participant by phone.

Review clinic-administered forms (*7, 10, 17, 39, 44, 45, 80, 81, 82, 83, 84, 85,* and *100)* for:

- Responses omitted unintentionally.
- Answers that do not follow the specified skip pattern.
- Codes/answers incorrectly marked or circled.
- Inconsistencies between questions.

Review self-administered *Forms 35, 38,* and OS Follow-up *Forms 145, 146, 167,* etc. for problems that would interfere with scanning, such as incomplete erasures and multiple marks. You do not need to edit these forms for incorrect skip patterns or inconsistent answers and you do not need to contact the participant to obtain missing response.

In addition, review mark-sense forms for:

- Stray pencil marks.
- Incorrectly filled or unfilled bubbles.
- Torn or soiled edges that may cause the form to be rejected by the scanner.
- Incomplete erasures.

See *Section 10.2.3.2 – Pre-Scan Edit* for detailed instructions for reviewing *FFQs*.

Review *Forms 10A, 17A, 33,* and *33D for:*

- Responses omitted unintentionally.
- Answers that do not follow the specified skip pattern.
- Codes/answers incorrectly marked or circled.
- Inconsistencies between questions.

Return incomplete forms to a staff person so that they can contact the participant and fill in incomplete information.

18.2.4 Editing Forms

18.2.4.1 Editing Key-Entry Forms

Do not erase data on key-entry forms. Instead, draw a line neatly through the wrong answer, mark or enter the correct one, and place your initials and the date next to the correction. Indicate whether the changed answer is an update of a previously entered correct response or a correction of an error. For coded answers, draw a line through the incorrect code and print the correct code above the wrong code (or mark the correct box if a checkbox question). Use colored ink instead of pencil for making edits.

After reviewing self-administered forms with participants, interviewers record their staff ID codes on the forms. Data coordinators and other data entry staff cannot make changes to these forms. Any problems should be returned to the interviewer for resolution.

The data entry system is set up so that certain routine checks of the data are made at the time of entry at the CC. A warning message is displayed on the screen if a value is outside of the expected range. Warning messages may be overridden by pressing the enter key. A "fatal" error occurs when a value that is not an "allowable response" is entered in WHILMA (for example, a text response is entered when a numeric value is expected). You must delete the incorrect response and enter a correct response before proceeding with key-entry of the form.

18.2.4.2 Editing Mark-Sense Forms

When editing *FFQs*:

- Completely erase any incorrect answers and bubble in the correct answer.
- Remove stray pencil marks.
- Do not write any comments in the margin of the *FFQ*.
- Use white correction fluid to cover stray or incorrect marks that cannot be erased.

When editing other mark-sense forms:

- Before scanning: follow the same editing guidelines as for the *FFQ*.
- After the form has been scanned once, don't change the bubbled items if you are only updating a few responses. Instead:
    1. Write the correct response in the margin along with your initials and the date.
    2. Indicate whether the change is an update or correction.
    3. Give the form to the data entry person who will key-enter the changes.

18.3 Data Entry

As mentioned previously, data enter WHILMA in one of three ways: key-entry from forms, scanning of mark-sense forms and direct data entry (without a form).

Following participant visits to the CC, forms are kept in the participant's file during data entry (except for pending test/specimen forms which may be stored in a central area of the CC to await results).

18.3.1 Data Entry Workspace

Each staff person involved in data entry should have adequate work space to keep participant files and data forms separated according to where they are in the data entry process. It is recommended that each data entry staff person maintain participant files-in-process in these categories:

- Incoming participant files from the CC or "problem" participant files returned by interviewers after resolution.
- Active forms ready to be scanned or key-entered or in process of being key-entered.

In addition, file space is needed for "loose sheets," that is, data forms that are processed outside of the participant's file, for example forms used for specimen tracking (see *Section 18.1.1 - Specimen Tracking*). Loose sheets should also be sorted by the above categories: ready to be reviewed, ready to be (or in the process of being) entered or scanned.

Depending upon how a CC is set up, the following items may be useful in the Data Entry area:

- An "urgent" box, containing participant files for women who have a visit scheduled in the very near future. This would contain files of participants that require priority data entry attention.
- A mailroom-like set of "pigeonholes" or bins labeled with the names of various CC staff members. Files requiring review and attention by the various staff members would be stored here.

18.3.2 Direct Data Entry

Information that will be recorded using direct data entry (without a form) includes:

- Current Medications and Current Supplements
- Medication dispensing (HRT and CaD)
- Medication adherence (HRT and CaD)
- Medication inventory

Paper forms will be provided for back-up in case the computer is not functional, except for selecting HRT and CaD medication bottles for randomized participants and Medication Inventory which can only be done by the computer. For additional information on direct data entry, consult *Vol. 5 - Data System, Section 7 - Data Entry*.

18.3.3 Scanning of Mark-Sense Forms

Scannable forms include *Form 35 – Personal Habits Update*, *Form 38 – Daily Life*, and *Form 60 - FFQ*. (Others may be developed in the future.) If mark-sense forms do not need to be scanned immediately, they will be placed in the participant's file before sending the file to Data Entry.

18.3.4 Key-Entry

Incoming participant files from the CC can be divided between data entry staff members if there is more than one data entry staff person. Each data entry staff person is responsible for reviewing the files they will key-enter or scan. The following process is recommended:

1. Review all participant forms for completeness and/or accuracy as appropriate (see *Section 18.2.3 - Review of Forms*).
2. Return participant files with problems to the interviewer or clinical staff responsible. The entire participant file should be returned to the interviewer or clinical staff, even if only one or two forms have problems. Problem areas should be clearly flagged (self-adhesive notes are useful). It is recommended that problem participant files be stored in a central area in the CC where they are available to clinicians and interviewers, but where they won't be mistaken for completed participant files and filed by medical records staff. To aid in return of files to staff, it may help to set up bins labeled with names of individual staff members. Files needing attention by various staff members can be placed in these bins. Effort should be made to keep participant files in this central area rather than on individual staff members' desks, except when the files are being reviewed.
3. Problems with participant files are resolved by the appropriate staff persons and returned with flags intact to the data entry staff person who originally reviewed the file. The data entry person then only needs to review the flagged pages since the others were reviewed previously. These returned files will be added to the top of files to be entered, so that "oldest" data is always entered first.
4. After participant files are reviewed and problems resolved, the forms are entered or scanned by a data entry staff person. Enter only those tasks that have been done. Do not enter encounter data for missed tasks. This includes forms and procedures that are required but have been "refused by the participant. Exceptions are:
   - If a *Form 44 – Current Medications* or *Form 45 – Current Supplements* is required, but at a visit, the participant is not taking any medications and/or supplements, it is appropriate to enter the encounter information with no medication (or supplement) data.
   - When a participant is having a procedure done outside of the CC (such as a mammogram) or is awaiting results of a Pap smear, it is acceptable to complete the encounter portion of the form and enter it into WHILMA before the results are received. This allows you to use the empty encounter as a tracking device in conjunction with the *Missing Labs Report (WHIP0782)*. These empty encounters should be deleted if the procedure wasn't done or the results will not be available.
5. After entry, the data entry staff person records their initials next to the "K" (to indicate key-entry of a keyed form) or "S" (to indicate that a scannable form has been scanned) on the front page of the form. Once a form is entered, CC staff should not make changes to it without notifying data entry staff. Storage areas for forms and files in the key-entry process must be clearly labeled to avoid accidental disturbance by other staff members. Forms should be entered as soon as possible after they are completed, to reduce the risk of the form getting lost or being missed by data entry staff.
6. After data entry is complete and all problem areas resolved, active CT and OS participant files are sent to the file room for filing. Forms and files for participants who become ineligible during the screening process can be stored separately. If data from ineligible participant's screening forms has been entered into WHILMA, the forms can be discarded. If you do not data enter the forms, they can be archived. Individual participant's files can be condensed and placed in storage boxes in the interest of saving space.

Signed informed consents for ineligible participants should not be discarded before the end of the study. No forms for randomized or enrolled participants should be discarded. Off-site storage for archived files must be readily accessible.

18.3.4.1 Key-entry of Specimen/Test Forms

To facilitate the reconciliation of WHILMA data with subcontractor data, enter all of the following forms into WHILMA for specimens that you collect and procedures that you perform.

- *Form 86 – ECG*
- *Form 87 – Bone Density Scan* (Bone density sites only)
- *Form 100 – Blood Collection and Processing*
- *Form 101 – Urine Collection and Processing* (Bone density sites only)

Note: Form 100 must be entered into WHILMA even if local lab results are not received. You do not need to enter local lab results into WHILMA for participants who dropped out of the study before randomization or enrollment.

18.3.5 Data Security

Staff using WHILMA should log completely out of WHILMA when vacating their workstations and when leaving for the day. Minimizing WHILMA on the task bar does not provide adequate security.

Information contained in participants' files is accessible to all CC staff, but should be maintained in a manner that allows adequate control and tracking of the location of the participant file and prevents unnecessary access to confidential participant information.

Participant files must be accessible for CCC chart audits. If a CC has had a chart audit since mid-1998, the CCC will usually only audit forms from follow-up visits and will not need access to screening forms. However, corrections to older forms may need to be made for CCC central analysis.

Only WHI staff may have access to participant files and WHILMA data. Each staff member must sign a confidentiality statement, agreeing not to disclose any WHI participant information to persons outside of WHI without a signed authorization from the participant.

Non-WHI staff, including ancillary study coordinators may not have access to participant data unless there is a specific release form signed by the participant granting access to the data.

18.4 Quality Assurance

Data management procedures and processes are monitored on-site for quality by CCC Quality Assurance personnel. See *Section 19 - Quality Assurance* for a detailed listing of data management operations that are reviewed during site visits. WHI data quality is monitored centrally at the CCC.

In addition, CCs can run reports from WHILMA that help monitor the quality of data management. Please see *Vol. 7, Table 5.2 – CC Schedule for Data Monitoring (Required)* for a list of WHILMA reports to use in monitoring data quality.

Another helpful report is the *Timeliness of Key Entry (WHIP0774)* report. Clinical Centers can print this report and determine whether they meet the "acceptable" standard of 80% of all self-administered forms entered within two weeks of collection. The report is broken down by form, so that CCs can identify problems with specific forms.

CCs are encouraged to perform routine audits and data verification on a randomly selected sample of charts. The *Questionnaire Responses Report (WHIP0104)* can be printed from WHILMA and compared with the original WHI forms in the chart to identify data entry mistakes. Other things to watch for when auditing participant charts are listed in the document “Chart Audit Codes” which can be found in the “QA Resources” Public Folder of the Microsoft Outlook e-mail system.

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Section 18
Data Management

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SECTION 20

SPECIAL POPULATIONS CONSIDERATIONS

INTRODUCTION

An important goal of WHI is to recruit and retain a representative sample of postmenopausal women of various ethnic, racial, and socioeconomic backgrounds. This includes women with low literacy levels, visual problems, or other conditions that may challenge their ability to participate. Regardless of whether a Clinical Center (CC) has been designated as a minority site, it is expected that the sample from each CC will include women from a variety of backgrounds. This section on special populations considerations is written as a guide to facilitate CC staff to optimally address the needs of women with a variety of experiences and backgrounds. It recognizes that women will be included in the study who have differences that must be considered as they are recruited and participate in the study.

This section begins with a general discussion of special considerations in cross-cultural counseling and interactions. Information is provided regarding cultural values, beliefs, and behaviors that need to be considered when counseling and interviewing participants as well as suggested approaches for maximizing successful cross-cultural interactions. The special needs of older women are presented, followed by those of women of ethnic minorities. General issues that need to be considered with all minority group women are presented as well as special considerations for women from specific minority groups. The reader is cautioned that these general characterizations may not apply to all minority women. These guidelines are simply meant to offer perspectives that will aid in dealing with these subgroups of women more sensitively, thereby encouraging participation, and adherence, with the study protocols. It should also be noted that some of these issues may be relevant as well for women who are not minorities. This section also considers approaches that should be used with women with special needs.

The final part of this section includes the "Guidelines for Translating Documents into Spanish." Several CCs have been identified to recruit Hispanic participants and require the Spanish version of WHI documents. This information is included as a matter of record of how WHI documents were translated into Spanish and for reference by CCs in the translation of CC-specific documents.

20.1 Special Considerations in Cross-Cultural Counseling and Interaction

One key to cross-cultural counseling is an understanding of value systems in other cultures and their influence on health and nutrition. Every culture has a value system that directs behavior by setting norms.

20.1.1 Cultural Values

A value is a standard that people use to assess themselves and others. It is a widely held belief about what is important and desirable for well-being. Working with participants from diverse backgrounds requires understanding your own values as well as the values of other groups. Too often we interpret the behavior of others as negative because we don't understand the underlying value system of their culture.

There is a natural tendency for people to be "culture bound," to assume that their values or customs are more sensible and right. Cross-cultural counseling and interaction presents special challenges because they require you to work with participants without making judgments as to the superiority of one set of values over another.

To enhance your understanding of cultural differences in values the following list provides a general comparison of Traditional American values with values commonly found in some other countries.

Traditional American Values	**Other Cultures' Values**
Personal control over environment	Fate
Change and variety	Tradition
Competition	Cooperation
Individualism	Group welfare
Future orientation	Past orientation
Directness	Indirectness/"Face"
Informality	Formality
Time Importance	Human interaction importance
Duration of life	Quality of life

Examples of Potential Differences in Values

- Participants and health-care staff may differ on the value of time. Most of us are ruled by time schedules. If "being on time" and "not wasting time" are not familiar concepts to the participant, a 9 o'clock appointment may not be kept until 10 or 11 o'clock. This may be considered entirely appropriate behavior.
- Decisions regarding medical screening or food intake might not be decided by the individual, but by group or family agreement. Thus, a woman may not follow the practices suggested because of extended family values and traditions.
- A woman may not believe that her health habits are related to well-being, but rather attribute them to "fate." Thus prevention will be viewed as a "waste of one's time."

20.1.2 Health Beliefs

Cultures vary in their beliefs of the cause, prevention, and treatment of illness. These beliefs dictate the practices used to maintain health. The value of "good health" is also variable. The traditional American culture emphasizes duration of life, whereas some other cultures place greater emphasis on the quality of life.

A woman may follow a specific process in seeking health care. Family is much more important in some cultures. The family supports and is frequently involved in the treatment, unlike Western medicine where the person is dealt with as a separate individual (not a part of a larger family).

20.1.3 Approaches to Dietary Change

Eating is a personal matter and people will change other aspects of their lives such as clothes and language first, and food habits last. Assure participants that traditional American foods are not necessarily better choices than their own culture's food choices.

For some ethnic groups, respect for authority and politeness in public may prevent a woman from raising questions about the study or the dietary change required. You may need to ask several times if there are any questions about the study or diet program.

The degree of compliance may be hard to evaluate and assure. If a woman's values are inconsistent with the underlying rationale for the recommended change, the probability of noncompliance is high. Women may agree to do something out of courtesy or fear, but may have no intention of following through with the study recommendations. Limited understanding of health issues may act as a disincentive for participant compliance, particularly for preventive measures.

20.1.4 Non-Verbal Communication

Your personality and communicating style affect the counseling process. The women may easily detect attitudes you think you are concealing. Genuine interest and concern for the woman are essential qualities for CC staff members during cross-cultural counseling and interaction.

Messages are communicated by facial expressions and body movements which are specific to each culture. You should be aware of variations in nonverbal communication to avoid misunderstandings or inappropriate movements which may unintentionally offend participants. Also, you should use caution in interpreting the woman's facial expressions or body movements. Your interpretation may be quite different from the woman's intent.

- Silence. You may view silence as awkward, however, other cultures are quite comfortable with periods of silence.
- Distance. The most comfortable physical distance between you and another person varies from culture to culture. The typical American generally prefers to be about an arm's length distance away from another person. Hispanics usually prefer closer proximity than most Americans. Giving the woman options for space preference, such as saying "Please have a seat wherever you like," can help you establish the proper distance for that person.
- Eye Contact. The amount of eye contact that is comfortable varies with each culture. Many Americans are brought up to look people straight in the eye. However, older Black Americans may have been taught not to make eye contact with whites. Staring is considered impolite in some groups. However, if you avoid eye contact, or break eye contact too frequently (e.g., as you fill in forms) it may be misinterpreted by the participant as disinterest.

  Observe the participant when listening and speaking. It can offer clues to appropriate eye contact. You can also arrange to sit next to potential participants, rather than directly across from them, to reduce eye contact.

- Facial Expression. Expression of emotion between people of different cultures varies from very expressive, as with Hispanics, to total non-expressiveness, as with Asians. Many Americans have a tendency to regard people who are more expressive as immature and those with less expression as unfeeling.
- Body Language. The position, gestures, and motion of the body can be interpreted differently depending on the culture. The use of hands is a common vehicle for nonverbal expression. A firm handshake may be a positive gesture of goodwill in the Anglo-American culture, but some other cultures prefer only a light touch. Standing with hands on hips may imply anger to some participants. Pointing or beckoning with a finger may appear disrespectful to some cultures.

Conservative use of body language is wise when you are uncertain as to what is appropriate within a cultural group. Observing the woman's actions and interactions with others may give you direction for acceptable body language. Being open with participants and asking general questions about body language can also help if you have doubts about appropriate behavior.

- Verbal Communication. How you speak is as important as what you say in cross-cultural interactions. Your tone of voice should be positive, avoiding condescending, disinterested, or unpleasant tone. The volume should be audible, but not so loud as to make the woman feel uncomfortable. Often we mistakenly assume that a louder voice is clearer and therefore more easily understood by the participant. Articulate each word and adjust your rate of speech, if necessary. Speech that is too rapid might not be understood, while speech that is too slow might actually bore the woman.

  Don't try to imitate an ethnic communication style which is not naturally your own. For example, using Black American language and communication style, when you are not Black American, may be interpreted as ridicule.

- Formality. Anglo-Americans tend to be informal in their verbal communication, but some other cultures prefer to keep a relationship more formal. Don't assume a first-name basis is appropriate for client relationships. Many Black Americans may view being addressed by their first name as too familiar and may infer disrespect. With any participant, terms of endearment such as "honey," etc. should be avoided. Asking the woman how she prefers to be addressed is the easiest solution, or assume formality when in doubt.
- Rapport. It is important to establish rapport with the participant when beginning the visit. Use "small talk" to reflect genuine concern for the woman. However, too much chatting, too many questions, or being "too nice" may cause uneasiness or raise suspicion.

20.1.5 Getting Accurate Information

All staff are concerned with getting accurate information from participants, and this is multiplied when the interaction is cross-cultural. Finding approaches that get better information is easier once you are aware of some additional barriers to communication.

Possible Barriers

There are several reasons why a participant of a different culture may not provide a staff member or counselor with good information.

- Lack of trust;
- Participant feels the information you want is inappropriate;
- Participant is uncomfortable with age, sex, education level, or race of the counselor or staff member; and
- Participant will make an effort to "please" the counselor or staff member.

Suggested Approaches

- Establish rapport and show genuine concern.
- Ask questions in several different ways to double-check information.
- Adjust style of interaction to complement differences in age between you and participant.
- Use open-ended questions.

20.1.6 Preparing for Cross-Cultural Counseling or Interaction

- Understand your own cultural values and biases.

- Acquire basic knowledge of cultural values, health beliefs, and nutrition practices for participant groups you routinely serve.
- Be respectful of, interested in, and understanding of other cultures without being judgmental.

20.1.7 Enhancing Communication

- Ask how the participant prefers to be addressed.
- Allow the participant to choose seating for comfortable personal space and eye contact.
- Avoid body language that may be offensive or misunderstood.
- Choose a speech rate and style that promotes understanding and demonstrates respect for the participant.
- Avoid slang, technical jargon, and complex sentences.
- Use open-ended questions or questions phrased in several ways to obtain information.

20.1.8 Promoting Positive Change

- Build on cultural practices, reinforcing those which are positive, and promoting change only in those which are harmful.
- Check for participant understanding and acceptance of recommendations.
- Remember that not all seeds of knowledge fall into a fertile environment to produce change. Of those that do, some will take years to germinate. Be patient and provide counseling in a culturally appropriate environment to promote positive health behavior.

Information adapted from: "Cross Cultural Counseling: A Guide for Nutrition and Health Counselors." USDA, US Department of HHS, FHN 250, September 1986.

20.2 Working with Older Women, Ethnic Minorities, and Women with Special Needs

20.2.1 Older Women

Recognize the diversity and heterogeneity of older women: They will vary widely on dimensions of health and functional status, educational background, standard of living, and cultural background. The potential for certain health problems increase with advancing age.

20.2.1.1 Health and Functional Impairments

Problems:

- Vision and hearing may be impaired.
- Cognitive impairments such as memory, performance and certain dimensions of intelligence may decline with age. The speed at which information is processed may also be slower. The woman may have difficulty retrieving relevant information.
- May easily fatigue, sometimes become confused.
- May become emotionally distressed (cry) because questions asked evoke sad memories.

Solutions:

- Select a private environment that is free of distractions, extraneous noise, interruptions, etc.
- Appeal to the woman's altruism. Tell her that participation is important for future generations.
- Speak slowly, clearly, provide redundant cues (position yourself so that they can both see and hear you speak). Use the low frequency range of your voice; do not yell.
- Be alert for signs of fatigue. If possible, give the woman a brief rest period. Reschedule, if necessary.
- Strike a balance between compassion and objectivity.
- Repeat questions and response categories.
- Do not overload the woman with information.

20.2.1.2 Personality and Motivational Factors

Problems:

- May be less interested in general in topics of the study and may object to the relevance of certain types of data for the study.
- May be more readily influenced by interviewers and more susceptible to interview bias.
- Ethnic/cultural group differences may be more extreme.

Solutions:

- Clearly identify yourself and don't keep the woman waiting.
- Emphasize the importance of the study and the need for questions and procedures.
- Be sensitive to bias and try not to express opinions.
- Recognize differences in communication styles (language) among different ethnic groups.

20.2.1.3 Cohort Differences (Life Experience Effects)

Problems:

- On average, today's older women have fewer years of formal education than younger women and have encountered fewer tests and standardized interviews.
- May disregard standardized scale formats.
- May sidestep questions and converse "on the side." Information that older women have to report is inherently more complex because they have a lifetime to summarize.
- May misunderstand questions or response options.
- May have different standards about the appropriateness of being asked for certain types of information (e.g., income data; functional status data).
- May be more easily insulted at being asked particular questions (e.g., ability to stand from a chair when answer seems obvious).

Solutions:

- Explain carefully and simplify the procedures to be used and the reasons for using them.
- Give the woman a road map of what will happen, how long it will take.
- Anticipate and address participant fears and anxieties about questions being asked, procedures being used.
- Clarify questions and response options using language more familiar to the woman as needed.
- Explain that sensitive information will not be reported at the individual level; only group data will be reported.
- Emphasize the importance and value of the data to be collected and how it will help current and future generations, etc.
- Emphasize that while some questions may not be appropriate to them, they have to be asked of everyone.
- Promise to provide (and follow through) general information about the study as a whole as it becomes available.

20.2.2 Women from Minority Groups

20.2.2.1 Ethnic/Racial Sensitivity

Problems:

- May have a preference for interacting with individuals who are representative of own minority group.
- May want to participate with a friend but due to randomization scheme they may not be assigned to same group.
- May not have a personal physician or system of regular medical care.
- May be uncomfortable in groups where there are no other individuals from own racial/ethnic group.
- May perceive members of own minority group to be more aware of and sensitive to life circumstances, perspectives and concerns.
- May perceive lack of employment of individuals from minority groups on clinic staff as an indication of prejudice.

- May become offended if it appears that they or others from ethnic/racial minority groups are treated differently or are not respected.
- Published statistics and information on minority community may not be accurate.
- There may be varying perspectives and experiences in ethnic subgroups within African-American, Hispanic, Native American, and Asian minority groups.
- More likely to eat ethnic foods, special spices, seasonings, etc.

Solutions:

- Make sure staff, particularly receptionist, is pleasant, respectful, and positive.
- Do not let a woman wait for an extended period of time in the CC.
- Stress that participation in WHI does not replace the need for regular medical care.
- Select a staff that is representative of the community and that reflects a balance of ethnic/racial groups.
- Have a staff member of the same ethnic/racial background of the women available to explain study protocols, consent forms, and questionnaires.
- Appoint a local advisory committee; include reputable minority community representatives. Ensure that members are clear about their role and level of involvement.
- Become thoroughly familiar with minority community characteristics, information channels, and power structure.
- Recognize the diversity of ethnic viewpoints within minority subgroups that can influence responses to the study protocols.

20.2.2.2 Personality Motivational Factors

Problems:

- May perceive research as a form of exploitation in which non-minority individuals reap the benefits.
- May be concerned about being used as a "guinea pig" in research.
- May believe that only minority scientists should study minority populations.
- May have past history of being exploited by sales people under the guise of a survey or research study.
- May be less prone to self-disclosure in research, particularly to someone from another ethnic or racial group.

Solutions:

- Explain that the study will provide important information for all women of all ethnic and racial backgrounds.
- Note that women from all ethnic and racial groups are included in the study.
- Inform the woman that researchers from all ethnic and racial groups from across the country are involved in conducting the study.
- Have a staff person of the same ethnic and racial background of the woman available to explain information and to assist in completing questionnaires as needed.
- Present study through public forums, such as churches, community associations, fraternal groups, and in ethnically-focus newspapers.

- Obtain sponsorship of various individuals or organizations that have a reputation of showing concern for the welfare of the minority community.
- Use the media to inform and motivate the community about the study.
- Send letter about project on official agency stationery before initial contact. If initial contact is in person, have identification available from official agency.

20.2.2.3 Cohort Differences (Life Experience Effects)

Problems:

- On average, recently immigrated minorities have less experience in completing tests and questionnaires.
- May not be familiar with questionnaires that have items with multiple response options, rating scales, or "skip to" item designations.
- May be reluctant to provide personal information, particularly of a sexual nature.
- May be wary of researchers misusing information.

Solutions:

- Explain why personal and sexual information are asked on questionnaires.
- Explain how to complete forms and how to respond to items and rating scales.
- Tell the woman to ask questions about items that she does not understand. Have someone available to answer questions.
- Explain that information collected during study will only be used for study purposes.

20.2.3 African-American (Black)

Problems:

- May be quite religious. May not readily accept interventions or actions that are perceived to be against God's will or God's plan in nature.
- More likely to believe in destiny.
- May put a high degree of trust in personal physician regarding all health matters.
- May not participate in health research without the perceived support of physician or regular health care provider.

Solutions:

- Explain carefully and simply the procedures and interventions to be used and the reasons for using them.
- Anticipate and address participant questions about the naturalness of replacing hormones after menopause.
- Inform local health care providers about the study and that some of their patients may be involved.

20.2.4 Hispanic

Problems:

- May not feel comfortable speaking English.
- May seek informal approval from husband or older son for decision making.

- May be concerned that personal information (for example, income or immigration information) will place family at risk.
- May be suspicious of government involvement in a research project if family members have lived in oppressive societies with government informers.
- May assume that WHI will replace regular medical care.

Solutions:

- A staff person bilingual in Spanish and English should make initial contacts with potential participants in minority Hispanic CCs. Receptionist and preferably Clinic Practitioners (CPs) should be bilingual.
- If the person answers the telephone in Spanish, the staff person calling should continue the conversation in Spanish.
- Use the formal and respectful form of the pronoun "you" in Spanish, that is, "usted," when talking to Spanish women.
- The husband or older son, if a husband is not available, should be informed about the study to encourage their informal permission.
- Carefully explain the confidentiality of information obtained in the study.
- Assure the woman that personal information will not be provided to other government agencies.
- Explain that personal data will not be reported at the individual level; only group data will be reported.
- Send letter to health care provider about woman's participation in WHI. Stress that the family doctor or health care provider will continue to provide usual care.

20.2.5 Native American

Problems:

- May not be comfortable speaking English.
- May prefer to have a family member present during interview.
- May not accept interventions that are not readily understood or visibly demonstrated to contribute to health problems.
- May not readily accept health care services from non-Indian health service provider or urban Indian health program.
- May associate certain health problem as "normal" part of aging which do not require medical intervention.
- May de-emphasize personal health problems or complaints.

Solutions:

- Provide a trained interpreter or interviewer who speaks the language.
- Where appropriate, accept the presence of other family members during the interview.
- Explain with illustrations how interventions work to prevent disease or improve health.
- Work with local Indian Health Service or Native American health care providers to develop referrals and follow-ups.
- Explain that not all symptoms are caused by aging.
- Explain why it is important to maintain health for the benefit of self and especially for the family unit.

20.2.6 Asian

Problems:

- May be highly concerned about personal social status issues.
- May not readily provide information that could be perceived to shame or reflect poorly on self, or family members.
- May hesitate to respond to questions about income, educational level, living arrangements, and household composition.

Solutions:

- Assure the woman that all information is confidential and that personal information will only be reported as group data.
- Explain why information on income, education, and family background are important to the study.

20.2.7 Women with Special Needs

Problems:

- May not be able to read or write English or Spanish well.
- May not be able to see well enough to read or complete study forms alone.
- Mobility may be compromised.
- May not be able to complete study forms without assistance.
- May require additional time for completion of study forms.
- May become frustrated and discontinue participation.
- May have child care responsibilities for grandchildren or other young children that may interfere with participation.

Solutions:

- Let women know that assistance can be provided in completing forms if they require it, at CC discretion.
- Provide assistance if possible in completing study forms for women who have a low literacy level, visual problems, or physical mobility problems. Ensure that answers recorded are those of the woman, not of the person providing assistance.
- Women who are illiterate are excluded from the study at CC option.
- Exclude volunteers who can not speak in local CC languages or dialect. Only use translators who are part of the bilingual CC staff or volunteer translators for which levels of fluency in both languages are known to be satisfactory.
- Identify women who require assistance in completing study forms during the initial Screening Visit (SV0 or SV1). Check a form that has been completed in the CC by the woman. Incomplete forms, inappropriate responses, or an unusually long period of time completing forms indicate that a woman is likely to need assistance.
- Designate a family member or person in the household to aid women who require assistance in completing study forms at home if one is available. Clearly identify designated person, note on CC forms, and train in approach to providing assistance. Training should emphasize having the designee focus on obtaining and recording the woman's response and <u>not</u> their own. Items on questionnaires that

are sensitive or may be embarrassing to provide answers to family member should be completed in the CC with the assistance of CC staff rather than with assistance of family member.

- Women in the dietary change group who need assistance in completing study forms and participating in DM intervention may remain in this group if they are able to name a family or household member to aid them. Designees should be informed of the commitment required, trained, and encouraged to attend dietary change sessions that are necessary to understand proper completion of forms.
- Assist women with limitations in mobility with arranging transportation to and from the CC.
- Assist women with child care responsibilities; help plan or arrange child care during CC visits.
- If CCs cannot provide assistance for women with inadequate literacy skills and if the woman cannot designate a helper to assist with all aspects of the CTs, she is ineligible.

20.3 Guidelines for Translating Documents into Spanish

These guidelines for Spanish language translation address:

- Translation of documents for which there is no previous Spanish translation;
- Materials used in health promotion projects, with particular focus on multi-center trials; and
- Checking the acceptability of previously translated documents.

Guidelines for Translation:

1. Document is translated by a Native Spanish-language translator, who is skilled in grammatical rules and localized regionalisms. The translation will be entered on a computer with Spanish-language capabilities, including spell-check and thesaurus. All target audiences and their particular regional Spanish will be taken into account, including U.S. Border, Mexican, Central and South American, Caribbean (Cuban, Puerto Rican, Dominican) and Peninsular (Spain). A low literacy audience must be taken into account.
2. The first draft is proofread and reviewed by the translator. The document is to be read word by word, line by line to insure accuracy. During this review, the translator scans for errors, general syntax, and readability.
3. The first draft of the translated document is edited by a fully bilingual English/Spanish editor, who was not involved with the original translation of the document. They will have complete command of Spanish and be skilled in grammatical rules and localized regionalisms. All target audiences, and their particular regional Spanish, will be taken into account, including U.S. Border, Mexican, Central and South American, Caribbean (Cuban, Puerto Rican, Dominican) and Peninsular (Spain).
4. All changes by the editor are incorporated, and a second draft is completed. Closely scrutinized proofreading is now performed to correct any remaining grammatical/typographical errors.
5. The second draft is reviewed by designated Spanish-speaking reviewers who are involved in the use of the translated document and who are expert in the content of the original document. Ideally, these reviewers shall: (a) be expert in representing all of the affected subgroups in the target area; (b) keep in mind the goals of the intended message and the target audience; and (c) avoid re-translating the document, by merely changing the style of the piece or by replacing one correct word with another equally correct word. These reviewers will be provided brief summaries of the target population, including Hispanic subgroups, education, language preference and standards.
6. Only the appropriate reviewers comments are incorporated into the document. Although reviewers are sometimes expert on the content, they may or may not be capable of effectively representing all Hispanic subgroups. In addition, these reviewers, capable experts in their own fields, may not be "communications" experts. What might be appropriate by the reviewers standards may not be appropriate for the target audience.
7. A pilot test with the target audience is done if time and money permit.
8. When differences in opinion occur among the reviewers, broadcast-standards in the Spanish language will prevail. It is recommended that the input of Broadcast experts be considered in settling all differences.
9. A third and final draft is created, incorporating Broadcast input. This draft is submitted to the editor(s) for final proofreading and editing.
10. Another draft is prepared on a compatible computer diskette to produce galleys to reduce typesetting errors.
11. Galleys are carefully proofread by the editor(s).
12. Local Hispanic CCs should determine items or sections on forms with which Hispanic women voice confusion or difficulty.

13. Items or sections of forms with which difficulty is noted should be carefully documented, and specific written recommendations for changes should be sent to the Clinical Coordinating Center (CCC).
14. If applicable, incorporate suggested changes from local CCs into a final draft. The final draft should be reviewed by bilingual editor(s) before typesetting.
15. Final galleys are carefully proofread.

Section 20
Special Populations Considerations

Table of Contents

Appendix B

Abbreviations, Terms and Definitions

B.1 List of Abbreviations

BMD - bone mineral densitometry

BMI - body mass index

BSE - breast self-exam

CABG - coronary artery bypass grafting

CaD - Calcium and Vitamin D

CARET - Carotene and Retinol Efficacy Trial

CBE - clinical breast exam

CC - Clinical Center

CCC - Clinical Coordinating Center

CDP - Coronary Drug Project

CEE - conjugated equine estrogen

CES-D - Center for Epidemiologic Studies - Depression

CHD - coronary heart disease

CHF - congestive heart failure

CHRU - Cardiovascular Health Research Unit

CHS - Cardiovascular Health Study

CM - Clinic Manager

CSI - cholesterol saturated fat index

CT - Clinical Trial

CVD - Cardiovascular Disease

DA - Dietary Assessment

DC - Data Coordinator

DM - Dietary Modification

DMV - Department of Motor Vehicles

DSMB - Data and Safety Monitoring Board

ECG - electrocardiogram

ERT - estrogen replacement therapy

FDA - Food and Drug Administration

FFQ - Food Frequency Questionnaire

FHCRC - Fred Hutchinson Cancer Research Center

FIT - Fracture Intervention Trial

4DFR - Four-Day Food Record

FSMP - See WHT-FSMP

GPO - Government Printing Office

HCFA - Health Care Finance Administration

HDLC - high density lipoprotein cholesterol

HDL2 - high density lipoprotein subfraction 2 cholesterol

HDL3 - high density lipoprotein subfraction 3 cholesterol

HRQL - health-related quality of life

HRT - hormone replacement therapy

ICD-9 - International Classification of Diseases, Version 9

ICD-0 - International Classification of Diseases for Oncology

IND - Investigational New Drug

IOM - Institute of Medicine

IRB - Institutional Review Board

IRS - Inquiry Reporting System

LAN - local area network

LDH - lactic dehydrogenase

LDLC - low density lipoprotein cholesterol

Lp(a) - lipoprotein (a)

MAO - monoamine oxidase

MFA - monounsaturated fatty acids

MI - myocardial infarction

MPA - medroxyprogesterone

MRI - magnetic resonance imaging

MRL - Medical Research Laboratory

NCI - National Cancer Institute

NDI - National Death Index

NDS - (University of Minnesota) Nutrition Data System

NHLBI - National Heart, Lung, and Blood Institute

NIH - National Institutes of Health

NP - Nurse Practitioner

OMB - Office of Management and Budget

ORWH - Office for Research on Women's Health

OS - Observational Study

OSHA - Occupational Safety and Health Administration

P:S - polyunsaturated to saturated fat ratio

PA - Physician Assistant

PC - personal computer

PCP - primary care provider

PEPI - Postmenopausal Estrogen/Progestin Intervention Study

PERT - progestin/estrogen replacement therapy

PFA - polyunsaturated fatty acids

PI - Principal Investigator

PSA - Public Service Announcement

PTCA - percutaneous transluminal coronary angioplasty

QA - quality assurance

RBC - red blood cell

RC - recruitment coordinator

RDA - recommended daily allowance

S/C - sub-committee

SEER - Surveillance, Epidemiology, and End Result

SFA - saturated fatty acids

SOF - Study of Osteoporotic Fractures

SV0 - Screening Visit Zero

SV1 - Screening Visit 1, first screening visit

SV2 - Screening Visit 2, second screening visit

SV3 - Screening Visit 3, third screening visit

TC - total cholesterol

TG - triglyceride

TIA - transient ischemic attack

UM-NCC - University of Minnesota's Nutritional Coordinating Center

VCC - Vanguard Clinical Center

WAN - wide area network

WBC - white blood cell

W/G - working group

WHI - Women's Health Initiative

WHI PAC - Women's Health Initiative Program Advisory Committee

WHT-FSMP - Women's Health Trial - Feasibility Study in Minority Populations

B.2 List of Terms and Definitions

adherence - the degree to which a participant takes the prescribed study medications; one of three components of retention.

adverse effect - an undesirable physical or psychological change, occurring while a participant is receiving study intervention; it may or may not be attributable to that intervention.

alert - any physical finding, lying outside normal ranges or normal expectations, that requires follow-up; classified as requiring routine, urgent, or immediate referral.

ancillary study - an investigation based on information from the WHI Clinical Trial or Observational Study participants that is not described in the WHI protocol and involves data that are not collected as part of the routine WHI data set or biologic specimens for analysis or storage.

anthropomorphic measures - measurements dealing with size; weight or proportions; height and weight; waist and hip measurements.

arm - a treatment defined for a clinical trial component.

barcode - a set of parallel black lines used to represent a series of numbers or letters.

batch - a set of data or jobs to be processed in a single group.

bone densitometry centers - three CCs that perform bone densitometries on their participants, including those in the OS.

bulletin - official update to WHI Manuals from CCC.

CaD participant - a woman randomized to either arm of the CaD component of the WHI.

Calcium and Vitamin D component (CaD) - one of the three components of the WHI Clinical Trial comparing calcium and vitamin D to placebo for effects on disease incidence.

certification - documentation that a WHI staff member has demonstrated qualifications to perform a designated study task; a formal process of training and testing to assure the competency of study personnel.

Clinic Manager - designated, centrally trained CC staff person who is primarily responsible for the training/quality assurance of many of the clerical and support staff and interviewers.

Clinical Coordinating Center (CCC) - the WHI organization that has primary responsibility for overall coordination, quality assurance, data management, and analysis activities required for execution of the study as well as providing scientific advice and counsel for the design, conduct, and analysis of the CT and OS.

Clinical Center (CC) - a WHI organization responsible for the recruitment and management of WHI participants at a specific site.

clinical measurements - physical and performance assessment of WHI participants by CC staff; does not include measurements that require equipment such as ECG or bone densitometry.

Clinical Trial (CT) - the randomized WHI Clinical Trial consisting of three intervention components (DM, HRT, and CaD) to be tested singly and in combination with the others.

clinical trial - a research activity that involves administration of a test treatment to some experimental unit to evaluate the treatment.

cohort - a group of people defined by a common characteristic or set of characteristics.

comparison arm - the DM participants who are randomized to follow their usual diet.

component - one of the three clinical trials comprising the CT: DM, HRT, and CaD.

contact - any communication (written, telephone, or in-person) between a WHI participant or participant record and a CC.

control arm - CT participants randomized to the arm of a trial component that does not receive the dietary intervention (DM), or receives a placebo (HRT & CaD).

CT component - See trial component.

CT participant - a woman enrolled in any of the three components of CT.

current medication - any prescribed or over-the-counter drug or other supplement that a WHI participant is taking at the time of entry or at any other time in the study.

Data and Safety Monitoring Board (DSMB) - an independent board of scientists that regularly monitors WHI study progress, outcomes, and safety, and may make recommendations in regard to protocol changes.

Data Coordinator - centrally-trained CC staff person who is primarily responsible for maintaining the computer systems, data management and the training/quality assurance of CC data entry staff.

dietary change arm - the DM participants who are randomized to follow the intervention diet.

Dietary Modification component (DM) - one of the three CT components of the WHI designed to test the effect of a low-fat diet on incidence of disease.

DM group - a group of DM dietary change participants organized to meet together with a nutritionist at pre-determined times throughout the study cycle.

DM intervention participant - a DM participant who has been randomized to the intervention arm of the DM. (The DM component is the only one of the three WHI CT components that is unblinded).

DM participant - a woman randomized to either arm of the DM component of the WHI.

double blind clinical trial - a clinical trial in which the control and treatment arms are administered in identical fashion, and the actual treatment for a given participant is unknown by both the participant and the individual responsible for treatment.

eligibility criteria - conditions that a woman must meet to be eligible for a WHI study. Certain criteria (age, menopausal status, etc.) apply to all components, however, a trial component may also have its own criteria that a woman must meet to enter that study; encompasses both inclusion and exclusion criteria.

eligibility determination - a database function that evaluates all of a participant's data pertinent to a particular study component and summarizes her status.

encounter - an event in which an employee performs a task during a contact with a WHI participant.

endometrial aspiration - a clinical procedure in which a sample of the uterine lining is obtained; also known as an endometrial biopsy.

enrollment - the examination and data collection procedures associated with a participant's screening CC visits (pre-randomization visits). The participant is considered "enrolled" in a study component (OS, DM, HRT, CaD) at the time that her baseline and screening requirements (including randomization for CT components) have been met and documented the WHI database.

enrollment medications - single blind placebo pills taken by women interested in HRT to assess adherence prior to randomization.

Estrogen Replacement Therapy (ERT) - one of the three arms of the HRT component of the WHI.

exclusion criteria - existing conditions or factors that, for competing risk, safety, or adherence, make a woman ineligible for one or more of the WHI components. Ineligibility for one component does not necessitate ineligibility for all components. Also, certain criteria may be reevaluated at a later date, and, if they are no longer true, the woman may then be eligible.

exposure - the extent to which a person is subjected to a specific factor that may increase her or his risk of disease.

Fat Counter - a booklet containing a list of 1,100 foods and fat grams intervention women use to identify the grams of fat and calculate a fat score.

fat gram goal - the number of fat grams a participant aims to consume on a daily basis, based on self-monitoring, to reduce her fat consumption to 20% of total current calories. Each participant's goal is calculated using an algorithm based on height prior to randomization.

Fat Scan - a small booklet containing lists of food and corresponding grams of fat that DM intervention participants use as a quick self-monitoring method to monitor fat intake and calculate a fat score.

fat score - the average number of fat grams an individual consumes per day over a three-day period. This number can be calculated using a food diary with the Fat Counter or Fat Scan.

follow-up visit - a scheduled CC visit by a participant that takes place at a specified time post enrollment or randomization and is needed to collect follow-up data required by the protocol.

Food Diary - a booklet used by DM intervention participants to record the foods eaten during a designated number of days. The information recorded in the food diary is used to calculate the fat score using the Fat Counter. The Food Diary is similar to a 4DFR but the Food Diary is used as a self-monitoring tool during the first six weeks of DM intervention.

Food Frequency Questionnaire - self-administered assessment of participant's usual food intake over the previous three months (*Form 60*).

Food Record Inquiry - a request sent to a CC from the CCC for additional information on an incomplete or uninterpretable Four Day Food Record (*Form 68*).

form - any of a number of documents on which information regarding WHI participants is collected. This includes questionnaires on which a woman supplies information about herself and forms filled out by CC personnel.

Four-Day Food Record - a detailed documentation of food eaten over four days *(Form 62)*.

functional status - a woman's ability to perform activities of daily living based on her physical health; may be measured by physical performance measures or questionnaires.

guide edge - the side of a mark-sense form that aligns with the guide rail inside a scanner to ensure that rows of bubbles match exactly with the photocells in the scanner's read head. The timing track is always located along the guide edge.

Hormone Replacement Therapy (HRT) - one of the three trial components of the WHI designed to test the effect of ERT and PERT on disease incidence.

HRT Diary - a booklet that HRT participants fill out on a daily basis to record bleeding symptoms.

HRT participant - a woman randomized to any arm of the HRT component of the WHI.

inclusion criteria - existing conditions or factors that a woman must have to be eligible for the CT.

informed consent - the voluntary consent given by a participant in the study after being given information of the purpose, method of treatment, procedure for assignment to treatment, benefits and risks associated with participation, and required data collection procedures and schedules. Each of the three components of the CT and the OS have a separate informed consent form. An informed consent is a requirement in studies that are federally regulated or funded as well as by many state laws.

International Classification of Diseases, Version 9 (ICD-9) - a reference for abstracting and coding disease information.

intervention - an effort to prevent a disease or condition or to change the natural course of a disease or condition by attempting to alter the risk factors or precursors associated with the disease. In the WHI, intervention takes the form of hormone replacement, dietary modification, and calcium and vitamin D supplementation.

intervention arm - the dietary change intervention in the DM component.

Lead Clinic Practitioner - a centrally trained, licensed health care provider (physician, nurse practitioner, or physicians assistant) who is primarily responsible for training/quality assurance of clinical staff and whose scope of practice includes primary health care and women's health care in particular.

Lead Nutritionist - centrally-trained, CC staff person who is primarily responsible for the training/quality assurance of Dietary Assessment staff and/or Group Nutritionists.

leading edge - the end of a mark-sense form that enters the scanner first; where skunk marks are located.

litho-code - on mark-sense forms, an optional, binary-coded serial number unique to every form, usually accompanied by human-readable, decimal number equivalent.

local area network (LAN) - a configuration of computers whereby joint access to software and data are provided by a connection to a file server which stores all shared files.

medication - see study medication or current medication.

morbidity - an illness or some other health-related condition, except death.

mortality - death, usually verified through death certificates or some other reliable record of death.

National Cancer Institute (NCI) - a branch of the National Institutes of Health.

National Death Index (NDI) - a central registry of deaths, started in 1979 and operated by the National Center for Health Statistics of the United States Public Health Services.

National Heart, Lung, and Blood Institute (NHLBI) - a branch of the National Institutes of Health.

National Institutes of Health (NIH) - a group of institutes and related support structures located in Bethesda, Maryland, that is part of the United States Public Health Services. The NIH is responsible for funding basic and applied research in the health field; also initiates and carries out medical research on an intramural and extramural basis.

Nutrition Data System (NDS) - a microcomputer-based system for collection and analysis of dietary data. The NDS can be used to guide dietary recall interviews or to process written food records.

Observational Study (OS) - the component of the WHI in which women who are either ineligible for, or do not wish to participate in, the CT will be followed as a separate study to evaluate risk factors in women for the study outcomes.

OS participant - a woman enrolled in the OS of the WHI.

outcome - a health-related event of interest thought to be important in evaluating the effects of interventions of exposures; classified as primary or secondary depending on its relationship to the main study purpose.

participant - for the ease of writing and reading the WHI Manuals, any woman who meets basic study age and menopausal status requirements, and has agreed to at least one CC visit so screening can be performed, regardless of the outcome of the screening (i.e., women deemed ineligible for CT and OS who come to the SV1, randomized to any CT, or enrolled in the OS) are all participants. However, in preparing scientific papers and reports it is understood that a woman should be more definitively referred to as "potential participant" pre-randomization and a "CT participant" post-randomization, while a woman enrolled in the OS should be referred to as an "OS participant."

participant ID number - the unique 8-digit number assigned to a participant.

participation - the degree to which a participant performs the protocol defined tasks directed by the component to which she is enrolled or randomized; one of three components of retention.

performance - the degree to which a DM intervention arm maintains a low-fat diet; one of three components of retention.

placebo - a pharmacologically-inactive substance resembling a medication (in shape, texture, size, taste, etc.) given to participants randomized to the control arms of the HRT or CaD trial components; used to maintain the blinding of a participant and CC staff to the participant's treatment arm.

prescription - an order for hormones to be dispensed to a HRT participant in response to an adverse effect or nonsteroidal anti-inflammatory medications given to lessen discomfort of the endometrial aspiration.

primary care provider - a WHI participant's personal physician or other health care provider whom she sees regularly for routine health care.

Principal Investigator (PI) - term used by NIH to designate the individual responsible for the scientific content of a grant or contract-supported research project.

Progestin and Estrogen Replacement Therapy (PERT) - one of the three arms of the HRT component of WHI.

Project Officer - the NIH scientist responsible for oversight of scientific, administrative, and fiscal aspects of WHI and integration of participating NIH Institutes.

protocol - a narrative document that describes the general design and policies of a study.

quality assurance - procedures aimed at maintaining the protocol standards for WHI and evaluating WHI operations (at both CC and CCC) for deviation from the protocol.

questionnaire - a form that asks a number of questions on one or more topics and is generally filled out by a WHI participant and brought with her to a CC visit.

randomization - the process of assigning an individual to an arm (intervention/control) by a random method.

recruitment - the process of identifying and inviting a woman into the study for screening. Recruitment of a woman ends when either she attends the first screening visit or the CC determines it is not appropriate to invite her to schedule an SV1.

Recruitment Coordinator - centrally trained, CC staff person who is primarily responsible for the coordination of recruitment strategies, plans for informing and educating the medical and lay communities about WHI, and documenting monthly recruitment activities.

retention - the strategies and procedures CCs use to assure a participant's adherence, performance, and participation in the study.

satellite CC - a CC site that has operational ties but geographical distance from the main CC.

screening visits - visits by a participant to the CC which take place at or before randomization to CT or enrollment into OS and which are needed to collect eligibility or baseline data required by the study protocol.

session - a unit of instruction (self-contained educational material) that covers a single topic or a small section of a broad topic to aid in behavioral change. The material is designed to provide topic-specific information and recommendations to participants.

side effect - a physical or psychological change that is attributable to a study arm.

skunk marks - on a mark-sense form, a unique combination of black squares along the leading edge of the form that tells the scanner's computer which program to use in interpreting the forms.

study - a scientific endeavor designed to answer specific questions.

study medication - an drug, supplement, or placebo dispensed to a HRT or CaD participant.

study population - all women who are enrolled in either the CT or OS of the WHI.

symptom - a physical or psychological change reported by a participant.

target date - the specified date at which a contact (phone or CC visit) is required in accordance with procedures. The target date of routine follow-up contacts is based on the date of randomization.

timing mark - on a mark-sense form, a black rectangle that corresponds to a horizontal row of bubbles on a form.

timing track - on a mark-sense form, a series of timing marks that runs down the guide edge of a form and triggers the scanner's read head to read a row of bubbles.

transfer participant - a participant who was first seen at one CC and is later seen at another CC. This usually occurs because the participant moves to the new CC area.

trial component - any of the three intervention studies (DM, HRT, and CaD) that, along with the OS, comprise the WHI. Also CT component.

unblinding officer - an individual at each CC who is not involved in the ascertainment of outcomes. Should unblinding become necessary, the unblinding officer and the CC consulting gynecologist will be the only CC staff persons unblinded to the participant's treatment arm.

visit - a WHI participant's attendance at a CC for screening or follow-up purposes.

WHILMA - the WHI study database developed in the Oracle software system, and provided to each CC as well as the CCC.

WHI Manuals - the set of documents describing all key aspects of the conduct of this study.

Volume	1	Study Protocol and Policies
	2	Procedures
	3	Forms
	4	Dietary Modification Intervention
	5	Data System
	6	DXA Quality Assurance
	7	Quality Assurance

WHI participant - a woman who is enrolled in at least one component of the CT, or who is taking part in the OS.

WHI Staff - all persons employed by the WHI to perform the activities of the WHI studies. This includes CC, CCC, subcontractor, and NIH employees.

WHI Study - the CT (consisting of any of the three components: HRT, DM, & CaD), and the OS of the Women's Health Initiative.

wide area network (WAN) - a linkage of computers designed to allow joint access and transfer of files across long distances.

window - the time interval for performing a specified baseline or follow-up contact. The window for WHI follow-up visits is a 4-week period ($\pm$ 2 weeks) of the target date. For example, if a follow-up visit target date is 3-15-93, the visit window is 3-1-93 to 3-30-93.

Your New Eating Style booklet - a booklet given to randomized DM Intervention women who have been waiting at least one month for first group meeting.

Appendix B:
Abbreviations, Terms and Definitions

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