WAVE Study
Manual of Operations

April 1999

CONFIDENTIAL

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1. LIST OF ABBREVIATIONS

ASCUS	Atypical Squamous Cells of Uncertain Significance
CAL	Core Angiographic Laboratory
CBL	Core Biochemistry Laboratory
DDC	Drug Distribution Center
DSMB	Data Safety & Monitoring Board
HRT	Hormone Replacement Therapy
ICD	International Classification of Diseases
INR	International Normalized Ratio
IRB	Institutional Review Board
NHLBI	National Heart, Lung & Blood Institute
OTC	Over the Counter
RFP	Request for Proposal
SCC	Statistical (& Study) Coordinating Center

2. CLINICAL SITES IN WAVE TRIAL

2.1 INTRODUCTION

In order to begin participation in the WAVE trial it is necessary for each clinical center to be certified by the Study Coordinating Center (SCC). To obtain certification, each clinical center must:

1. Receive Institutional Review Board (IRB) approval and mail a copy to the NHLBI.
2. Identify a study coordinator.
3. Provide locked storage space for the drugs and confidential study documents. Provide adequate facilities for maintaining study collection data collection forms and other study documents and materials.
4. Attend a training session.

2.2 IRB APPROVAL PROCEDURE

As soon as the WAVE protocol is finalized the Principal Investigator (PI) of each center, or his/her designee, should submit the WAVE protocol with an informed consent form to his/her IRB. The sample consent form included in the protocol as Appendix A may be modified as needed to meet local IRB requirements. A copy of the IRB-approved informed consent form should be mailed to the NHLBI along with the letter of IRB approval before the clinical center begins screening patients.

IDENTIFICATION OF STUDY COORDINATOR

One individual at the clinical center should be identified as the study coordinator. The name, mailing address, FedEx address, telephone number, fax number, and E-mail address (if available) of this individual should be sent to the WAVE SCC. In order for each clinical center to function smoothly, it is critical that one responsible and resourceful individual be identified. Prior to the start up of the trial, a coordinator training session will be held. Attendance is mandatory and no clinic may begin recruitment until the coordinator attends the training session. The coordinator will be responsible for training any required additional staff at their clinic.

2.3 STUDY DRUG STORAGE

If the clinical center plans to use a local pharmacy for storing and distributing the WAVE medication, the local pharmacy must comply with the study requirements for receipt, storage, and distribution of the study drugs. It is the coordinator's responsibility to monitor drug inventory and to order additional drug supplies from the DDC. More information for initial ordering, re-ordering and disposal of drug supplies is contained in Chapter 9.

If the clinical center does not use a local pharmacy, the coordinator should have a secure cabinet for storage of WAVE study drugs and discuss the procedure with the SCC.

2.4 SPACE REQUIREMENT

The clinical center should have an appropriate space for the study coordinator to interview patients, complete data forms, and count and dispense medication. In this space or in an adjacent area there should be a secure cabinet for patient study forms. The forms should be stored in a secure area. Copies of completed forms must be kept until at least the WAVE study indicates they may be destroyed. However, local regulations may require retention of the study forms for a longer period. Each coordinator should know local regulations with regard to disposal of study documents.

2.5 OTHER EQUIPMENT REQUIREMENTS

A fax machine to receive information from the SCC and to send Wave screening forms to the SCC is required. For the baseline blood collection and storage, a freezer (-70c) which is not an autodefrost model is required to store plasma or serum samples. In some instances a -20c freezer is acceptable (please see chapter 11 on the Central Biochemistry Lab procedures for more details).

2.6 WAVE CLINIC NUMBERS

The following clinic number will be used on the patient study forms to identify the WAVE clinics.

CLINIC	Clinic Number
University of Alabama at Birmingham	1
Hartford Hospital	2
Medlantic Research Institute	3
Johns Hopkins Bayview Medical Center	4
Duke University Medical Center	5
University of Ottawa Heart Institute	6
Institut de Cardiologie de Montreal	7

3. PRE-RANDOMIZATION PROCEDURES

3.1 SCREENING

Candidates for the WAVE trial are screened to determine eligibility status. Each coordinator will monitor the daily catheterization laboratory logs and other potential sources, to identify likely candidates for the trial. The coordinators will be free to design an identification program that is efficient for their local conditions. However, it is anticipated that the initial identification of potential WAVE participants will be by: reviewing logs of diagnostic catheterizations; pre- and post- intervention catheterizations; reviewing existing databases to identify women from research programs.

Coordinators will maintain a screening log, in which screened candidates are sequentially recorded.
Once a potential participant has been identified, the first step is to obtain her informed consent. Additional procedures, such as approval of her cardiologist, may be required at your site.

3.2 INCLUSION CRITERIA

WAVE participants must meet the following criteria:

1. *Postmenopausal*
   For WAVE, a woman is postmenopausal if she meets *any one* of the following three definitions:
   a. Bilateral oophorectomy at any age
   b. Age 45-54 with FSH $\geq$ 40 IU/L
   c. $\geq$ 55 years of age

   Note that the date of last menses plays no role in this definition, and that women younger than 45 years cannot qualify unless they've been oophorectomized. No proof of age or past oophorectomy is required. If FSH is drawn to assess WAVE eligibility, the report should be filed at the clinical site (do not send it to the SCC). If no paper report of laboratory results is provided at your institution, document the FSH level in progress notes.

2. *Informed Consent*
   WAVE participants must be willing and able to provide informed consent. Surrogate consent is not acceptable. Consent process is described in section 3.4.

3. *Qualifying protocol angiogram within 4 months of randomization*
   Angiograms will be sent to the Angiographic Core Laboratory for confirmation of eligibility prior to randomization. A qualifying angiogram must:
   a. be performed according to the angiographic protocol described by the Core Laboratory,
   b. be of acceptable quality for quantitative analysis,
   c. be performed while the patient was hemodynamically stable, and
   d. must have at least one qualifying lesion.

A qualifying lesion is one with a 15-75% reduction in lumen diameter, and the artery with the qualifying lesion may not have been previously intervened, that is, subjected to the balloon dilatation, stent, atherectomy or other intervention. There is no time limit for intervention of the qualifying artery: intervention renders that vessel ineligible forever. However, if a diagonal branch was dilated, the participant may qualify with a lesion in the left anterior descending artery, and vice-versa.

If the qualifying angiogram was done within two weeks of an acute myocardial infarction, the qualifying segment may not be the infarction segment.

3.3 EXCLUSION CRITERIA

WAVE participants must have *none* of the following exclusion criteria:

1. *Concurrent Hormone Replacement Therapy*

   If women have been on HRT for *at least* three months when screened, it is advisable that they should wash out for three months before being eligible. Women who develop intolerable menopause symptoms while washing cannot be randomized.

   If a woman has been on HRT for less than three months, no specific washout period is required. If a woman was started on HRT for menopausal symptoms, the coordinator should ascertain that these symptoms will be tolerable if the participant is randomized to placebo.

   Women may use estrogen vaginal cream while on WAVE study medication if they use it no more than 25% of the time.

   HRT use is documented on form W02 (Medical History Form). Details of washout or ongoing estrogen vaginal cream use should be documented in progress notes.

2. *Concurrent vitamin C or E supplements*

   Women taking vitamin supplements exceeding the recommended daily allowance (RDA for vitamin C or E) must discontinue them to be eligible for WAVE. The RDA for vitamin C is 60mg/day and for vitamin E is 30 IU/day. No specific washout interval for vitamins is required. WAVE will provide Centrum Silver multivitamins for study participants if they wish to take a multivitamin. Use of other vitamins, eg. B complex or calcium plus vitamin D is allowed. Ask women to bring in all their supplements as well as prescription medications to their screening visit, and read the labels to ensure that supplements don't exceed the RDA.

3. *History of breast cancer or mammogram suggestive of cancer*

   Women with past history of breast cancer are ineligible. Women whose most recent mammogram is suggestive of breast cancer are ineligible unless they have a subsequent negative work-up. This may take the form of additional views, ultrasound, aspiration or biopsy. A woman is not eligible until documentation establishes clearly that breast cancer is no longer suspected.

   Document initial mammogram on form W05 (GYN Exam form). If referred for further evaluation, document in progress notes. If subsequent evaluation is mammographic, eg. extra views, complete the mammography section of another form W05, checking the "Other" box for visit type. Document other types of subsequent evaluation in progress notes and fill out form W18 and file reports of procedures and pathology in the participant's file at the clinical site.

4. *History of endometrial cancer without hysterectomy*

   Women with stage I endometrial cancer treated at least five years prior to randomization are eligible.

5. *Any abnormal uterine bleeding or endometrial hyperplasia*

   Baseline endometrial biopsies are not required for WAVE. Therefore, women with abnormal uterine bleeding are ineligible until they've been evaluated and treated for whatever conditions are identified. Women with known endometrial hyperplasia are ineligible until they've been treated and had a subsequent negative endometrial biopsy. As a practical

matter, if they've had prior endometrial hyperplasia on a regimen of estrogen plus progestin, they may not be good study candidates.

6. *Abnormal Pap smear*
   Women with dysplasia of grade CIN-I or higher are ineligible until treated. Those with atypical squamous (or glandular) cells of uncertain significance should be evaluated per standard of care, and are eligible while that evaluation is ongoing. There is no known relationship between HRT and cervical cancer.
7. *Uncontrolled diabetes or hypertension*
   Women with uncontrolled diabetes or hypertension are ineligible until these conditions are controlled. The definition of "controlled" hypertension or diabetes is by the judgment of the local investigators.
8. *Acute myocardial infarction less than four weeks prior to randomization.*
   Women with Q wave, non-Q wave or aborted myocardial infarctions cannot be randomized until four weeks after the myocardial infarction. In general, a myocardial infarction is defined for eligibility purposes by the presence of an appropriate ICD-9 code (see Appendix) for acute myocardial infarction on a hospitalization face sheet.
9. *Planned or prior coronary artery bypass surgery*
   Planned bypass surgery means a woman and her physician are definitely planning surgery.
10. *Fasting plasma triglycerides > 500mg/dL (5.65 mmol/L)*
    If a participant had fasting triglycerides measured within four months of randomization, that value may be used. If not, draw during screening. If multiple values available, use the most recent. If a proper laboratory report is provided, file in the participant's chart; if not, document level in progress notes.
11. *Serum creatinine > 2.0mg/dL (177mmol/L)*
    If a participant had creatinine measured within four months of randomization, that value may be used. If not, draw during screening. If multiple values available, use the most recent. If a paper laboratory report is provided, file in the participant's chart; if not, document level in progress notes.
12. *Symptomatic gallstones*
    If a participant has been told by a medical care provider that she has symptomatic gallbladder disease, she is ineligible unless she has a cholecystectomy.
13. *NYHA class IV congestive heart failure or known ejection fraction <25%*
    If a participant has congestive heart failure of such severity that she is dyspneic at rest, she's ineligible. If she's known to have an ejection fraction <25% by any imaging modality (contrast ventriculography, radionuclide ventriculography, echocardiography, gated SPECT) she's ineligible. WAVE does not require documentation of ejection fraction before randomization.
14. *History of hemorrhagic stroke or bleeding diathesis*
    Bleeding diathesis includes, but is not limited to, conditions such as idiopathic thrombocytopenic purpura or clotting factor deficiencies.
15. *History of pulmonary embolism or ideopathic deep venous thrombosis*
    Any prior pulmonary embolism excludes a participant. A woman with previous deep venous thrombosis may be eligible if she had a clearcut, temporary predisposing condition such as immobilization due to leg fracture.
16. *History of osteoporosis*

If a woman has been told by a medical care provider that she has osteoporosis, she's ineligible unless she is being treated with non-hormonal therapy, such as Fosamax or calcium/vitamin D. No bone density measurement is required for WAVE.

17. *Anticipated survival < 3 years*
    Serious medical conditions which, in the judgment of the investigator and coordinator, make the woman unlikely to survive until her exit angiogram exclude her from participation.
18. *Concurrent participation in another masked clinical trial*
    Women participating in interventional device trials or short term post-angioplasty anti-thrombotic trials are eligible so long as angiography is not part of the trial. If angiography is required, that study's exit angiogram can serve as the entry angiogram for WAVE. Participation in non-blinded trials is generally acceptable. Check with the SCC for questions about individual situations.
19. *Angiogram not meeting protocol criteria*
    Angiograms from potential participants will be sent to the WAVE Central Angiographic Laboratory. They will inform the clinic if the angiogram meets the WAVE criteria.
20. *Unlikely to adhere to the protocol in the judgment of the investigator*
    Issues such as substance abuse, dementia, psychosis, unsupportive home or family situation or other conditions rendering adherence and retention unlikely are covered by this exclusion criteria.

3.4 OBTAINING INFORMED CONSENT

Every clinical trial's success depends on the cooperative participation of its subjects. Participants must take their study medication as prescribed, return for follow-up visits as indicated, and contact their WAVE clinic if side effects develop. It is therefore imperative that we try to obtain truly informed voluntary consent. If the consent process is simply a mechanical ritual, the trial could be jeopardized not only on ethical grounds, but also by a high number of early drop outs and poor adherence to therapy.

3.4.1 BASIC ELEMENTS OF INFORMED CONSENT

According to Department of Health and Human Services (HHS) guidelines, informed consent is interpreted to mean:

> "The knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion."
>
> From the Code of Federal Regulations (Revised as of October 1, 1996)

The guidelines set forth eight basic elements of informed consent as follows:

1. A *statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedure to be followed, and identification of any procedures which are experimental.*
   The person obtaining consent must carefully call attention to the fact that this is a *research* study, rather than a therapeutic program specifically designed for the individual. Doses may be adjusted to reduce individuals' side effects from the study medication. Participants may discontinue study medication at any time for medical reasons or for any other reason,

although the trial cannot succeed unless a high proportion of participants remain on study medication.

Estrogen: The study drug Premarin has been licensed for hormone replacement therapy in the treatment of menopausal symptoms, atrophic vaginitis and osteoporosis (loss of bone mass) in postmenopausal women. Premarin is a mixture of natural estrogens derived from pregnant mares' urine. It contains estrone, equilin, 17-alpha-dihydroequilin, 17-alpha-estradiol, equilenin and 17-alpha-dihydroequilenin. Prempro has been licensed for these indications in women with an intact uterus. Addition of progestin to estrogen therapy significantly reduces the risk of endometrial hyperplasia, a possible precursor to endometrial cancer. In WAVE, women with a uterus will be randomized to daily Prempro (Premarin 0.625 mg plus medroxyprogesterone 2.5 mg) or to placebo. Women without a uterus will be randomized to daily Premarin (0.625 mg) or placebo.

Estrogen therapy may reduce coronary events in women with coronary artery disease. Meta-analyses suggest that women who use estrogen have fewer coronary events compared with women who never used estrogen, however, no adequately powered, randomized, placebo-controlled trial of estrogen has been completed.

Antioxidants: Vitamins C and E are available as over-the-counter vitamin supplements. Participants in WAVE will be randomized to vitamin C (500 mg bid) plus vitamin E (400 IU bid) or to vitamin C and E placebos.

2. *A description of any reasonably foreseeable risks or discomforts to the subject.*

Estrogen: Some patients may experience adverse reactions to estrogen, such as bloating, nausea, rash, headache, mood changes, breast tenderness or enlargement, or changes in blood clotting. Vaginal spotting or bleeding is common but usually resolves within several months. In some women, this spotting or bleeding may persist for a longer period of time. Additional medroxyprogesterone may be added if necessary to reduce or stop bleeding in women with endometrial proliferation due to estrogen. The participant should be told that for her safety, if she has severe or persistent bleeding, she may be asked to have an endometrial aspiration, in which a few cells from the lining of the uterus are sucked into a thin tube (about the width of a pencil lead) during a pelvic exam. Endometrial aspiration may cause stomach cramps. Fibroids (non-cancerous tumors of the uterus) may increase in size while taking estrogen. Estrogen use has been associated with a 2-fold increase in the risk of gallstones. Recent epidemiologic data indicates a 3-fold increase in the risk of blood clots in the legs and lungs. If a woman has had blood clots in her legs without clearcut antecedant cause, such as a leg fracture, or has ever had blood clots in her lungs, she is ineligible for the WAVE trial. Estrogen, when given alone, is also associated with an increased risk on endometrial cancer (cancer of the lining of the uterus). Medroxyprogesterone is therefore given with estrogen in this study to all women who have a uterus to protect against development of endometrial cancer. Prolonged use of estrogen may be associated with a slight increased risk of breast cancer. This slight increase in risk is the reason for the annual mammograms and breast exams performed as part of this study. Women with known breast cancer or endometrial cancer may *not* participate in this study.

Medroxyprogesterone: Side effects reported with medroxyprogesterone include breast tenderness, fluid retention, rash, depression or nausea.

Vitamins C and E are thought to be safe in the doses used in this study.

Procedures: Risks associated with angiography include a 1% (1 out of 100) chance of bleeding, a 0.1% (1 out of 1000) chance of a stroke, and a 0.05% (1 out of 2000) chance of death. The amount of radiation during heart catheterization is about 20 rads.

With coronary artery ultrasound, there is a risk of 0.3% (3 out of 1000) that a coronary artery may be damaged by the ultrasound device.

3. *A description of any benefits to the subject or to others which may reasonably be expected from the research.*
   Many participants will appreciate the opportunity to be involved in medical research relevant to women and to contribute to medical knowledge. The WAVE trial potentially benefits both the study participants and other postmenopausal women with coronary artery disease.

   Medications associated with the study will be provided at no cost to the patient. WAVE also provides free physical examinations, mammograms, laboratory blood analysis, and Pap smears during the course of the study. If one or both of the patient's heart catheterizations are done only for research purpose, WAVE will pay for the catheterization(s).

4. *A disclosure of appropriate alternative procedures or courses of treatment, if any that might be advantageous to the subject*.
   Explain to the patient that an alternative to joining this study is to take hormone replacement and/or antioxidant vitamins prescribed by her physician. However, neither has been demonstrated to reduce the size of plaque in the coronary arteries.

5. *A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.*
   Results will be given to the Study Coordinating Center for this research study at the George Washington University, and to the National Heart, Lung and Blood Institute. Neither the George Washington University nor the National Heart, Lung and Blood Institute will be provided with patient's names. The patients' medical and research records may also be provided to the Food and Drug Administration and the United States Department of Health and Human Services. Except for these entities, and any local IRB requirements, medical and research study records will be kept confidential unless the patient authorizes their release, or the records are required by law (i.e., court subpoena). Participating women will be identified by a unique WAVE study number.. Patient names will not be used on study forms. At the end of the study, the patient will be told what treatment group she was assigned to if she requests this information.

6. *For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.*
   The patient will be sent a bill for whatever medical care she requires. She will not be responsible for measures taken specifically for participating in the WAVE trial (e.g., semi-annual visits). All or part of the bill may be paid by the patient's health insurance. The National Heart, Lung and Blood Institute will not pay for the care. The patient should not expect anyone to pay her for any pain, worry, lost income, or non-medical care costs that may occur from taking part in the study.

7. *An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.*

The patient should be told that if she requires immediate medical care, she should go to an emergency room. Otherwise the doctor in charge of this study will take care of the patient or

help her get the care she needs. In the event of injury, the patient may pursue whatever appeals may be available under the law.

8. *A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.*
   It was recently announced in the Federal Register that the FDA had amended its regulations concerning informed consent. The regulation was effective December 5, 1996 and is not retroactive. The amendment includes:
   1. Informed consents must be signed by the subject or the subject's legally authorized representative and **must be dated by the subject or representative** at the time of consenting.
   2. Case histories must verify that the consent was signed prior to participation.

3.4.2 GUIDELINES FOR OBTAINING CONSENT

The following are guidelines to help ensure that consent is as informed and voluntary as possible:

1. Participants should be fully informed about the study and have adequate time to discuss the value and potential consequences of participation. If it is thought desirable, the consent form may be left with the patient after the initial contact, so that he or she may more carefully review it. However, it should be returned unsigned. Time should be set aside for eligible participants to discuss the pros and cons of participation.
2. Participants should be encouraged to discuss the study with anyone they wish, particularly family and friends who might be affected (e.g., persons who might be needed to provide transportation). Close associates of the participant may raise questions and considerations that the patient may have overlooked, and questions that concern the family are better answered sooner than later. Family support will generally improve patient cooperation and adherence.
3. To be eligible for participation in the WAVE trial, participants must have the capacity to give their own informed consent. If a participant is incapable of understanding what is expected of her as a subject in the study, it is not permissible to obtain informed consent from a guardian.
4. The setting in which consent is obtained should be as private as possible so patients can freely ask questions without embarrassment.
5. To avoid pressuring the patient, only one person associated with the study should be present when the patient reviews the consent forms. If a second witness is required, he or she should be as unobtrusive and non-committal as the situation permits.
6. The patient should be given a copy of the informed consent form after it is signed and witnessed.

3.4.3 STORAGE OF INFORMED CONSENT FORMS

All signed Informed Consent Forms should be kept at the clinical center in the patient's file. Do not send signed Informed Consent Forms to the SCC.

3.5 PRE-RANDOMIZATION PROCEDURES

Once informed consent has been obtained, the patient's eligibility must be verified and baseline information must be obtained before the patient can be randomized into the study. Clinical sites are free to organize pre-randomization procedures to best fit clinic flow, as long as the requirements of the study are met. The complete list of pre-randomization procedures required for the study follows:

1. Creatinine and fasting triglycerides must be drawn, unless they were assessed within four months of screening. If a new sample is needed, the patient needs to be instructed to fast (except for water) for at least 12 hours prior to coming to the clinic.
2. A limited physical exam is required. This will include a breast and pelvic exam, measuring height, weight, waist circumference, hip circumference and blood pressure. It will also include a pelvic exam and a Pap smear.
3. Blood samples should be collected for central analyses and for local assessment of INR if the woman is on Warfarin (Coumadin), (this may be done at the randomization visit).
4. If the patient has not had a mammogram within the previous 12 months, one should be scheduled, completed, and results reviewed before randomization.
5. If the patient has not had an ECG within four months of the expected date of randomization, one should be performed.
6. For patients participating in the SPECT/EET substudy, baseline measurements for the study need to be obtained.
7. For patients participating in the Brachial Reactivity substudy, baseline measurements for the study need to be obtained.
8. Information about the medical history of the patient is to be recorded on form W02.
9. Information about medications the patient is currently taking is to be recorded on form W05.
10. Schedule the randomization visit. If the patient did not already have a blood collection during the screening visit she should be asked to fast for at least twelve hours prior to the visit. A blood sample will be collected for central analyses. For women on warfarin (Coumadin), collect a sample for local assessment of International Normalized Ratio (INR).

3.5.1 PRE-RANDOMIZATION FORMS

The forms listed below need to be completed (prospectively) before the patient is randomized. Some of the required information may be provided by the patient, while other pieces of information will necessitate obtaining patient records.

- Form W02 (Medical History). See chapter 14 for details.
- Form W04 (Current Medications). See chapter 16 for details.
- Form W05 (Gynecological Examination). See chapter 17 for details.
- Form W10 (Seattle Angina Questionnaire). See chapter 10 for details on forms W10-W14, the quality of life forms.
- Form W11 (MOS-36 Health Survey).
- Form W12 (Duke Activity Status Index).
- Form W13 (CES Depression Scale).
- Form W14 (MOS Sleep Scale).
- Form W16 (Angiographic Procedure Form). See chapter 10 for details.
- Form W17 (Supplemental Angiographic Worksheet). See chapter 10 for details.

4. RANDOMIZATION PROCEDURE AND VISIT

4.1 OVERVIEW OF THE RANDOMIZATION VISIT

During the randomization visit, eligible participants are randomized into the study. The following are to be completed at this visit:

1. Eligibility of the participant is confirmed using sections A and B of form W03 (see chapter 15 for details).
2. The pre-randomization forms are reviewed to ensure that they are accurate and current. The forms are: the medical history form (form W02), the medications form (form W05), and the quality of life forms (forms W10 through W14-chapter 23).
3. The physical measures are obtained and the randomization checklist on form W03 is completed.
4. The automated randomization system at the SCC is called to obtain a randomization number and coded medication assignments for the patient. The randomization number and the medication codes should be recorded on form W03.
5. The study medications are dispensed. Each woman will be given a seven month supply of her study medications and a medication instruction sheet. Open label vitamins (Centrum Silver) are provided to patients who request them.
6. A bleeding diary is provided for those women with an intact uterus. Study handouts as well as handouts from NHLBI and the AHA may also be provided.
7. The patient is given the phone numbers of the local WAVE contacts, including the gynecological contact.
8. The one month visit is scheduled.
9. The randomization form (form W03) is faxed to the SCC as an independent confirmation of randomization.

Note that any information obtained before the randomization call is considered baseline or pre-randomization information, even if it is collected at the randomization visit. Likewise, any information obtained after the randomization call is considered follow-up information.

4.2 AUTOMATED RANDOMIZATION PROCEDURE

4.2.1 OVERVIEW

The randomization is done by telephone through the SCC's automated randomization system. This system is set up to run every day, 24 hours a day until randomization is completed. The person randomizing the patient will need to check that all pre-randomization procedures have been performed and that the pre-randomization forms have been filled out. The first three sections of form W03 (Randomization form) should also have been completed.

Before placing the call, the person randomizing the patient should make sure he or she knows the following:

- The WAVE center number of their clinic (1-5).
- The center's 4 digit security number. The automated telephone randomization system uses this number to keep unauthorized people from accessing the randomization lists. This number must be selected by the center and communicated to the SCC before the study starts.
- Whether the patient had a hysterectomy (this appears on forms W02 and W03).

4.2.2 CALLING THE RANDOMIZATION SYSTEM

The person randomizing the patient should call the Study Coordinating Center (SCC) telephone randomization system at (301) 984-7217. The system should pick up almost immediately. If after three rings, the system has not answered, contact the SCC staff (details below).

If a busy tone is heard, the system is currently being accessed by another center. Randomization calls last a minute to a minute and a half. If after waiting 5 minutes, the line is still busy, contact the SCC staff.

4.2.3 THE RANDOMIZATION PROCESS

Once the automated system answers, the caller will be asked to answer a series of questions. The normal sequence of questions is summarized in the figure below.

Randomization Sequence		
System	Hello, you have reached the automated randomization system for the WAVE trial. Enter your one digit center number.	
You	*Enter your one digit center number*	λ
System	You have selected center *[name of your center]*. Please enter your 4 digit identification code.	
You	*Enter the 4 digit code for your center*	λ λ λ λ
System	To randomize a new patient, press 1. To review the medication assignments of a previously randomized patient, press 2. To obtain the randomization numbers of the most recently randomized patients at your center, press 3.	
You	*Press 1*	∂
System	If the patient you are randomizing had a hysterectomy, press 1. Otherwise, press 0	
You	*Press 0 or 1*	λ
System	You are about to randomize the patient to the *[hysterectomy/no hysterectomy]* arm of the trial. To proceed with the randomization, press 1; to cancel the randomization, press 0.	
You	*Press 0 or 1*. ***Randomization occurs here, immediately after You press 1.***	∂
System	The randomization number for this patient is *[nnn]*. This patient is assigned hormone therapy kit *[H-nn/M-nn]*. To confirm, please enter the 2 digits you just heard after the *[H-/M-]*	
You	*Enter the two digits after the H- or M-*	λ λ
System	This patient is assigned vitamin kits *[C-nn]* and *[E-nn]*. To confirm, please enter the 2 digits you just heard after the *[E-]*	
You	*Enter the two digits after the E -*	λ λ
System	The randomization process is complete. Good-bye.	

The randomization system also gives you the opportunity to review which kits were assigned to a given patient. This may be used, for example, to verify the assignment at a follow-up visit where the patient is being given a refill.

Review Sequence		
System	Hello, you have reached the automated randomization system for the WAVE trial. Enter your one digit center number.	
You	*Enter your one digit center number*	λ
System	You have selected center *[name of your center]*. Please enter your 4 digit identification code.	
You	*Enter the 4 digit code for your center*	λ λ λ λ
System	To randomize a new patient, press 1. To review the medication assignments of a previously randomized patient, press 2. To obtain the randomization numbers of the most recently randomized patients at your center, press 3.	
You	*Press 2*	•
System	Enter the patient's 3 digit randomization number	
You	*Enter the randomization number*	λ λ λ
System	You have requested patient *[nnn]*. This patient is assigned hormone therapy kit *[H-nn/M-nn]*. To confirm, please enter the 2 digits you just heard after the *[H-/M-]*	
You	*Enter the two digits after the H- or M-*	λ λ
System	This patient is assigned vitamin kits *[C-nn]* and *[E-nn]*. To confirm, please enter the 2 digits you just heard after the *[E-]*	
You	*Enter the two digits after the E -*	λ λ
System	Good-bye.	

Finally, you can retrieve the randomization number of the last patients randomized in each of the two arms of the study (the hysterectomy arm and the no-hysterectomy arm).

Summary Sequence		
System	Hello, you have reached the automated randomization system for the WAVE trial. Enter your one digit center number.	
You	*Enter your one digit center number*	λ
System	You have selected center *[name of your center]*. Please enter Your 4 digit identification code.	
You	*Enter the 4 digit code for your center*	λ λ λ λ
System	To randomize a new patient, press 1. To review the medication assignments of a previously randomized patient, press 2. To obtain the randomization numbers of the most recently randomized patients at your center, press 3.	
You	*Press 3*	÷
System	The last patient to be randomized to the no hysterectomy arm of the trial in your center was *[nnn]*. The last patient to be randomized to the hysterectomy arm of the trial in your center was *[nnn]*. Good-bye	

4.2.4 CALL INSTRUCTIONS

During the call, the caller should wait for the question to be stated completely before keying in the answer (instead of "typing ahead".) This reduces the likelihood of keying mistakes. Pressing a key during a question does not interrupt the question, so there is no advantage to typing ahead. The system will wait 5 seconds after the end of each question for the first digit of the answer. If no digit is received within 5 seconds a warning is issued and the question is asked again.

A major issue the caller must be aware of is when it is safe to hang up. When randomizing a patient, the randomization is considered official as soon as you press 1 in answer to the question " *to proceed with the randomization, press 1; to cancel the randomization, press 0*". Hanging up at any time before that point effectively cancels the randomization. Once you have pressed 1, however, the patient is officially randomized to the study and the SCC randomization lists are updated accordingly.

If you are accidentally disconnected after the moment of randomization, but before you hear the patient's randomization number or medication kit assignments, you can call the randomization system and use the "summary" sequence to obtain the randomization number of the patient and the review sequence to obtain the medication kit assignments. Before calling the system again, however, wait about a minute to allow the computer to reset itself. Calling back too soon will result in a busy signal. In case of problems, please contact the SCC staff.

After the patient is randomized, a copy of the randomization form W03 should be faxed to the SCC by the end of the same working day as an independent confirmation of the randomization.

4.2.5 CONTACTING THE STUDY COORDINATING CENTER (SCC) STAFF

The automated randomization system is designed to remain in operation 24 hours a day. A backup battery will keep the system going in case of a power failure at the SCC. However, if the person randomizing the patient is unable to get through to the randomization system, or if problems are encountered during the randomization process, the SCC staff should be contacted. They can be reached at (301) 881-9260 during normal working hours. After hours they can be reached by pager. The pager number is: 1-202-592-8486.

After dialing the paging number, the caller will hear two short beeps. He or she should then *immediately* key the telephone number at which he or she can be reached (including the area code) and then press the pound key. The system will respond with a series of short beeps and then hang up. The SCC member on call will be carrying the randomization lists and will be able to randomize the patient by phone. If you are not contacted within 10 minutes of paging, please page again.

4.3 DISPENSING OF MEDICATION

At the randomization visit, each participant is assigned and dispensed 3 drug therapy kits (HRT/HRT placebo, Vitamin C/Vitamin C placebo and Vitamin E/Vitamin E placebo). In order to minimize the chances of error, the person dispensing the medication kits should be familiar with the way the kits are coded:

- Each kit has a code which consists of a letter, H,C,E,M, followed by a dash and a two digit number. For example, C-07.
- The letter at the beginning of the code dictates which medication the kit contains:
  - H- indicates unopposed HRT (active or placebo)
  - M- indicates HRT + medroxyprogesterone (active or placebo)

C- indicates vitamin C (active or placebo)
E- indicates vitamin E (active or placebo)

- The two digits that follow the dash will generally vary from one kit to the other. However, for any given patient, the same two digit number will be used for vitamins C and E. Thus, for example, an assignment for a woman with an intact uterus might be M-07, C-11, E-11. For a woman with a hysterectomy, a typical assignment might be H-03, C-05, E-05. Again, note that the numeric part of the codes for vitamins C and E always match.
- Once a woman has been assigned a particular set of codes at randomization, the same codes are used to refill her study medication for the duration of the study. When the patient returns for refills, she will be given medications with the same kit number. For example, a woman assigned kit, H-02, C-08, E-08 at randomization will receive the same three kits again at six months, one year, and so on. In particular, women with an intact uterus at randomization who undergo a hysterectomy in the course of the trial will continue receiving Prempro (i.e. an M-code) after the hysterectomy.

5. FOLLOW-UP VISITS

5.1 GENERAL DESCRIPTION

The follow-up contacts in WAVE include follow up visits at 1,3,6,12,18,24,30, and 36 months. Some women randomized early in the trial may have a 42 month visit. In addition to these visits, there is also an Exit Visit. The study activities for follow-up visits are described in this chapter.

5.2 ONE MONTH VISIT

5.2.1 WHAT TO DO BEFORE THE ONE MONTH VISIT

No preparations are needed for the one month visit. A call reminding the patient of the visit may be helpful.

5.2.2 WHAT TO DO DURING THE ONE MONTH VISIT

One of the major goals of the one month visit is to reinforce the relationship between the participant and the WAVE clinical staff, including her gynecological contact. During the visit:

1. Discuss any side effects the participant is experiencing. The bleeding calendar and any other gynecological side effects should be discussed with the gynecological staff. Options for the management of side effects should be reviewed.
2. For women on warfarin (Coumadin), draw blood for the locally assessed INR.
3. Document any clinical outcomes that have occurred since the randomization visit.
4. Schedule the three month visit. The patient should be informed that the three month visit will involve blood tests and that she should fast for twelve hours before coming to the clinic. Patients enrolled in the Brachial Reactivity substudy will undergo additional procedures at the 3 month visit.

5.2.3 STUDY FORMS TO BE COMPLETED AT THE ONE MONTH VISIT

- W07s (One and Three Month Follow Up). See chapter 5 for details.
- W08 (Gynecologic Follow up Form). See chapter 17 for details.
- If the dosage of the participant's medications is modified, form W06 (Change of Study Medications) should be completed. See chapter 18 for details.

- If the patient has had a study outcome since the randomization visit, form W09 (Study Outcomes) should be completed. See chapters 8 and 22 for details.

5.3 THREE MONTH VISIT

5.3.1 WHAT TO DO BEFORE THE THREE MONTH VISIT

The study coordinator should contact the participant before the visit to remind her to fast for at least twelve hours before coming to the clinic.

5.3.2 WHAT TO DO DURING THE THREE MONTH VISIT

During the three month visit,

1. Draw a blood sample for central analysis. For women on warfarin, draw a blood sample for INR assay.
2. Discuss any side effects the participant is experiencing. The bleeding calendar and any gynecological side effects should be discussed with the gynecological staff. Options for the management of side effects should be reviewed.
3. Any clinical outcomes that have occurred since the one month visit should be documented (chapter 8).
4. The six month visit should be scheduled.

For women participating in the brachial reactivity studies, additional tests will be done:

5.3.3 STUDY FORMS TO BE COMPLETED AT THE THREE MONTH VISIT

- W04 (Current Medications Form). See chapter 16 for details.
- W07s (Three Month Follow Up). See chapter 19 for details.
- W08 (Gynecologic Follow up Form). See chapter 21 for details.
- If the dosage of the patient's medications is modified, form W06 (Change of Study Medications) should be completed. See chapter 18 for details.
- If the patient has had a study outcome since the randomization visit, form W09 (Study Outcomes) should be completed. See chapters 8 and 22 for details.
- Quality of life forms W10 (Seattle Angina Questionnaire) and W12 (Duke Activity Status Index Form) should be completed for participants in the SPECT/EET substudy. See chapter 23 for details on Quality of Life Forms.

5.4 SIX MONTH VISIT

5.4.1 WHAT TO DO BEFORE THE SIX MONTH VISIT

The study coordinator should contact the patient prior to the visit to remind her to bring in all unused study medication and other supplements and prescription medications.

5.4.2 WHAT TO DO DURING THE SIX MONTH VISIT

During the six month visit,

1. Document any clinical outcomes that have occurred since the three month visit (chapter 8).
2. Count all unused study capsules or tablets. Dispense a new supply of study medication. Do not re-issue returned medication.
3. Discuss any side effects related to the study medication and give another bleeding calendar if necessary.
4. Schedule the first annual visit.

5.4.3 STUDY FORMS TO BE COMPLETED AT THE SIX MONTH VISIT.

- W07 (Follow up form). See chapter 20 for details.
- W08 (Gynecological Follow-up Form). See chapter 17 for details.
- If the dosage of the patients medications is modified, form W06 (Change of Study Medications) should be completed. See chapter 18 for details.
- If the patient has had a study outcome since the randomization visit, form W09 (Study Outcomes) should be completed. See chapters 8 and 22 for details.

5.5 ONE YEAR VISIT

5.5.1 WHAT TO DO BEFORE THE ONE YEAR VISIT

The study coordinator should contact the patient to remind her to bring all unused study medication and other supplements and prescription medicines to the visit.

5.5.2 WHAT TO DO DURING THE ONE YEAR VISIT

During the one year visit,

1. Document any clinical outcomes that have occurred since the six month visit. (chapter 8).
2. Count all unused study capsules or tablets. Dispense a new supply of study medication.
3. Obtain an ECG.
4. Make arrangements to obtain any mammogram report performed in the past 12 months, or schedule one if no mammogram has been done in the past year.
5. Perform a general physical exam including a breast examination and a pelvic examination. For women with an intact uterus, obtain a Pap smear (unless one was done during the past 12 months). Provide breast self-exam teaching.
6. Discuss any side effects related to the study and give another bleeding calendar if necessary.
7. Schedule the 18 month visit.

5.5.3 STUDY FORMS

- W05 (Gynecologic Examination Form). See chapter 17 for details.
- W07 (Follow up). See chapter 5 for details.
- W08 (Gynecological). See chapter 17 for details.
- If any gynecological abnormalities are found, form W18 should be completed (See chapter 17 for details)
- If the dosage of the patients medications is modified, form W06 (Change of Study Medications) should be completed. See chapter 18 for details.
- If the patient has had a study outcome since the randomization visit, form W09 (Study Outcomes) should be completed. See chapters 8 and 22 for details.

5.6 EIGHTEEN MONTH VISIT

5.6.1 WHAT TO DO BEFORE THE 18 MONTH VISIT

The study coordinator should contact the patient to remind her that she needs to:

1. Bring all unused study medication and other supplements and prescription medicines with her.
2. Fast for at least 12 hours before coming to the clinic.

5.6.2 WHAT TO DO DURING THE 18 MONTH VISIT

During the 18 month visit,

1. Document any clinical outcomes that have occurred since the twelve month visit.
2. Count all unused study capsules or tablets. Dispense a new supply of study medication.
3. Draw fasting study bloods for central analysis.
4. Schedule the second annual visit.

5.6.3 STUDY FORMS

- W07 (Follow up). See chapter for details.
- W08 (Gynecological). See chapter for details.
- If the dosage of the patients medications is modified, form W06 (Change of Study Medications) should be completed. See chapter for details.
- If the patient has had a study outcome since the randomization visit, form W09 (Study Outcomes) should be completed. See chapters 8 and for details.

Form W10 (Seattle Angina Questionnaire), Form W11 (MOS-36 Health Survey), Form W12 (Duke Activity Status Index), Form W13 (CES Depression Scale), Form W14 (MOS Sleep Scale). See chapter 23 for details on the quality of life forms.

5.7 TWO YEAR VISIT

5.7.1 WHAT TO DO BEFORE THE TWO YEAR VISIT

The study coordinator should contact the patient to remind her to bring all unused study medication, other supplements, and prescription medicines with her and to ask her to fast for at least twelve hours before coming to the clinic.

5.7.2 WHAT TO DO DURING THE TWO YEAR VISIT

During the two year visit,

1. Document any clinical outcomes that have occurred since the 18 month visit (chapter 8).
2. Count all unused study capsules or tablets. Dispense a new supply of study medication.
3. Make arrangements to obtain any mammogram report performed in the past 12 months, or schedule one if none has been done.
4. Perform a limited physical exam including a breast examination and a pelvic examination. For women with an intact uterus, obtain a Pap smear (unless one was done during the past 12 months). Provide breast self-exam teaching.
5. Schedule the 30 month visit.

5.7.3 STUDY FORMS

- W05 (Gynecologic Examination Form). See chapter 17 for details.
- W07 (Follow up). See chapter 5 for details.
- W08 (Gynecological). See chapter 17 for details.
- If any gynecological abnormalities are found, form W18 should be completed (See chapter 17 for details)
- If the dosage of the patients medications is modified, form W06 (Change of Study Medications) should be completed. See chapter 18 for details.
- If the patient has had a major outcome since the randomization visit, form W09 (Study Outcomes) should be completed. See chapters 8 and 22 for details.

5.8 THIRTY MONTH VISIT

5.8.1 WHAT TO DO BEFORE THE 30 MONTH VISIT

The study coordinator should contact the patient prior to the visit to remind her to bring in all unused study medication, supplements and prescription medications.

5.8.2 WHAT TO DO DURING THE 30 MONTH VISIT

During the thirty month visit,

1. Document any clinical outcomes that have occurred since the 24 month visit.
2. Count all unused study capsules or tablets. Dispense a new supply of study medication.
3. Schedule the third annual visit.

5.8.3 STUDY FORMS TO BE COMPLETED AT THE 30 MONTH VISIT.

- W07 (Follow up form). See chapter 20 for details.
- W08 (Gynecological Form). See chapter 21 for details.
- If the dosage of the patients medications is modified, form W06 (Change of Study Medications) should be completed. See chapter 18 for details.
- If the patient has had a major outcome since the randomization visit, form W09 (Study Outcomes) should be completed. See chapters 8 and 22 for details.
- Form W10 (Seattle Angina Questionnaire). See chapter 23 for details on all quality of life forms (W11, W12, W13, and W14,).
- Form W11 (MOS-36 Health Survey). During this visit, the MOS-36 will be filled out twice, the second time for the response-shift analysis.
- Form W12 (Duke Activity Status Index).
- Form W13 (CES Depression Scale).
- Form W14 (MOS Sleep Scale).

5.9 THREE YEAR VISIT

5.9.1 WHAT TO DO BEFORE THE THREE YEAR VISIT

The study coordinator should contact the patient to remind her to bring all unused study medication, supplements and prescription medications with her and to ask her to fast for at least twelve hours before coming to the clinic.

5.9.2 WHAT TO DO DURING THE THREE YEAR VISIT

During the three year visit,

1. Document any clinical outcomes that have occurred since the 30 month visit. (chapter 8).
2. Count all unused study capsules or tablets. Dispense a new supply of study medication.
3. Draw a blood sample for central analysis
4. Make arrangements to obtain any mammogram report performed in the past 12 months, or schedule one if no mammograms have been done in the past year.
5. Perform a general physical exam including a breast examination and a pelvic examination. For women with an intact uterus, obtain a Pap smear (unless one was done during the past 12 months). Provide breast self-exam teaching.
6. Perform an ECG.

7. Schedule the Exit angiogram (note that for some women, the final angiogram will need to be scheduled at the 42 month visit).

For women enrolled in the SPECT/EET substudy, additional tests will be performed.

5.9.3 STUDY FORMS

- W05 (Gynecologic Examination Form). See chapter 17 for details.
- W07 (Follow up). See chapter 20 for details.
- W08 (Gynecological Follow Up Form). See chapter 21 for details.
- If any gynecological abnormalities are found, form W18 should be completed (See chapter 17 for details)
- If the dosage of the patients medications is modified, form W06 (Change of Study Medications) should be completed. See chapter 18 for details.
- If the patient has had a study outcome since the randomization visit, form W09 (Study Outcomes) should be completed. See chapters 8 and 22 for details.

5.10 FORTY-TWO MONTH/EXIT VISIT

This visit will take place after the final angiogram. During the visit, the study coordinator should:

1. Discuss the results of the angiogram.
2. Discuss treatment options until the entire cohort is unmasked at the end of the trial.
3. Discuss the procedure for informing the patient and her designated physician of the trial's results.
4. Assess adherence, collect unused study medication.
5. Assess outcomes since the last visit.

5.10.1 STUDY FORMS

- W07 (Follow Up Form). See chapter 20 for details.
- W09 (Outcomes Form). See chapters 8 and 22 for details.

5.11 ADDITIONAL FORMS

In addition to the scheduled times, the following WAVE forms may be filled out as needed:

- W05 (Gynecologic Exam). This form is normally filled out at the annual visits, but can be filled out at other times as needed. See chapter 17 for details. If a gynecologic abnormality is found, form W18 should be completed.
- Form W07M (Missed Visit). This form is completed whenever a W07, a W08 or both are not available because the patient missed a semi-annual visit, or if a patient misses her annual visit and there is no W05.
- W09 (Outcomes form). This form reports patient study outcomes, including death, invasive cardiovascular procedures, occurrence of cancer, or hospitalizations. The form should be completed as soon as the outcome is known. In practice, the study coordinator is likely to find out about most outcomes at one of the scheduled study visits. In some cases, however, the study coordinator may be informed of outcomes between study visits. See chapter 8 and 22 for details.

- W15 (Protocol Deviation). This form is filled out whenever a protocol deviation is uncovered. See chapter 24 for details.
- W18 (Gynecologic Follow up). This form is completed whenever a gynecologic abnormality is referred for follow up, and whenever a patient is still bleeding at the 6 month visit. See Chapter 26 for details.

5.12 SUMMARY OF FORMS

Form	1 month	3 month	6 month	1 year	18 mo.	2 year	30 mo.	3 year
W05				X		X		X
W07			X	X	X	X	X	X
W07S	X	X						
W08	X	X	X	X	X	X	X	X
W10		X			X		X	
W11					X		X	
W12		X			X		X	
W13					X		X	
W14					X		X	

6. ASSESSMENT AND MANAGEMENT OF SIDE EFFECTS

6.1 ASSESSMENT OF SYMPTOMS

Management of side effects is based on the philosophy of protecting the safety of the participant while at the same time making every effort to adhere to the study protocol. It is important to obtain reliable information on all side effects if possible.

6.2 MANAGEMENT OF SIDE EFFECTS

6.2.1 GENERAL INFORMATION

Every effort should be made to prevent interruptions of study medication, or deviations from study protocol except where the patient's safety is affected. Trial participants may be at increased risk for adverse effects related to study interventions. These may range from mild inconvenience to life-threatening illnesses, including cancer or possibly death. Early identification of potential adverse experiences is essential to appropriate, prompt management of these conditions.

6.2.2 SIDE EFFECTS OF HORMONE REPLACEMENT THERAPY

Adverse effects are not uncommon among women taking hormone replacement, but not all women will have symptoms. In fact, women on placebo may also report symptoms. The severity

severity and frequency of symptoms will vary among women, as will the responsiveness of symptoms to hormone dose or regimen changes. During screening, participants should be educated about the various possible minor adverse effects that may occur. Adherence and retention of study participants will be enhanced through education of participants during screening. Tell each woman that these symptoms are in most cases not harmful, but she should contact the coordinator with any concerns. Reassure her that the minor symptoms associated with HRT usually resolve spontaneously within 6-12 months of starting the medications.

Minor symptoms: Initial management of minor symptoms consists of palliative treatment, with the goal of keeping the participant in the original treatment arm. Palliative measures should be tried for a month, if possible, before stepping down the dose of study medication.

- **Bleeding** - Over half of women with a uterus will report vaginal bleeding as a consequence of endometrial proliferation induced by the estrogen. Women should be told that bleeding in the first 6 months is a normal part of their body's adjustment to the study medication. Most women who bleed will have less and less bleeding over time. Women should be instructed to contact their coordinator if they have more bleeding than a normal period. They should also call if they have bleeding beyond 6 months post-randomization. *Women who have had a hysterectomy should report any vaginal bleeding promptly*.
- **Breast tenderness and swelling** - Women on HRT may find their breasts feel sore or swollen. Although this symptom is uncomfortable, it is rarely serious and usually goes away with time. Women can try decreasing their salt and caffeine (coffee, tea, caffeinated colas, chocolate) intake. Increased water consumption may also help. Coordinators may also recommend that women check the fit and support of their bras. Sometimes wearing a supportive bra, even to bed, helps decrease the tenderness.
- **Headaches** - Women occasionally report mild headaches on HRT. *If women have blurred vision, nausea and vomiting or weakness or tingling in any part of their body, they should call their coordinator right away*. Otherwise women should try their usual headache remedy, such as resting in a darkened room or taking an over-the-counter medication like acetaminophen, ibuprofen or aspirin.
- **Weight gain** - Some women worry that taking the study pills will make them gain weight. Randomized trials of HRT have estimated that groups of women taking placebo gained the same amount of weight during 3 year follow up as groups of women taking HRT.
- **Fluid retention, bloating or changes in bowel habits** - If women (feel they) are retaining water on study medication, palliative measures include reducing salt intake (bacon, potato chips, snack foods) and adding less salt to cooking or food at the table. If women report constipation, recommend increased intake of water and high fiber foots such as fresh fruits and vegetables and whole grain cereals and breads. Over-the-counter (OTC) fiber supplements (like Metamucil) may also be helpful. Increasing activity or exercising more may also be helpful.
- **Mood change or trouble sleeping** - There may be days when women report feeling a little sadder, angrier or more worried. These feelings may result from many different occurrences in their lives. Encourage women to work on any life problems: eat right, get a good night's sleep, or participate in some relaxing activity. It may also help to decrease caffeine or alcohol intake. Women may try starting a mild exercise program, like walking or stretching, and taking more time for social activities. For sleeping problems, decrease caffeine intake before bed, plan a relaxing bedtime routine like taking a warm bath and avoid heavy meals in the late evening.

- **Nausea -** Occasionally women report nausea after starting study medication. This usually subsides within the first 2 months. Women may try taking their study pills at bedtime or with food.
- **Vaginal discharge -** Counsel participants to expect a change in vaginal discharge on study medication. This may represent normal fluids and secretions. *If women report a foul odor, itching, dysuria, irritation or burning, they should be referred for evaluation of possible infection*. Women may also have persistent irritating discharge due to atrophic vaginitis. They may be treated with a non-estrogen vaginal lubricant (Replens, Astro-Glide, Lubron, K-Y jelly) initially. If the symptoms remain concerning, topical estrogen may be prescribed for no more than 3 months/year without unblinding.

At scheduled visits or unscheduled contacts, review noted symptoms and record frequency, duration and severity in progress notes. Provide reassurance and advice based on guidelines above. Tell the participant that these symptoms are not life-threatening, but that she should re-contact the coordinator if the symptoms become very uncomfortable or severe or if she is concerned. If appropriate, arrange to re-contact the participant for follow up.

Step-Down Dosing: Participants' dose of study HRT medication may be reduced to improve symptoms which are not ameliorated by palliative measures. Although a month-long attempt at palliative treatment is recommended, it's preferable to step-down dosing earlier rather than have participants stop study medication completely.

- The initial step-down is to reduce the dose to 5 days/week, eg. Monday through Friday. Complete the change of medications form, W06, each time the dose is changed, and document the change and reasons for change in progress notes. Arrange to re-contact the participant in one month, or a different appropriate interval, to see if symptoms are improved.
- If the participant tolerates the altered dosing, gradually advance back to the daily schedule, e.g. 6 days/week for two weeks, then 7 days/week. If this is not tolerated, the participant may be maintained on whatever dose is tolerated. If the participant does not tolerate 5 days/week, dose may be further reduced. Complete form W06 for each dosage change.
- On rare occasions, minor symptoms may necessitate unblinding of the consulting gynecologist. The participant should not be unblinded.

  If the participant is on active medication, the gynecologist will decide whether to adjust study medication dose or to discontinue study medication altogether. If the participant is on Prempro, the consulting gynecologist can switch the participant to daily Premarin with a reduced frequency of medroxyprogesterone 2.5 mg, such as 5 days/week or every other day. The minimum acceptable medroxyprogesterone dose for women with uteri is three 2.5 mg tablets per week. The participant should be reevaluated at appropriate intervals with an eye to resuming standard dosing as tolerated.

  If the participant is on placebo, she should be referred to her primary care provider for evaluation of the symptoms.

Menopausal symptoms: Some women may develop menopausal symptoms such as hot flashes or night sweats. As for HRT-related minor symptoms, palliative measures such as cool, light clothing, avoiding stressful situations and reassurance should be tried for one month.

If this is ineffective, HRT study medication can be doubled (2 tablets/day) for one month. If menopausal symptoms persist, discontinuation of HRT study medication may be necessary. Even Even if the participant goes on open label HRT, she may be able to resume study medication sometime later in the course of the trial. If doubling study medication is effective in reducing

menopausal symptoms, the higher dose may be continued for 2 months, at which point an effort should be made to decrease the dose.

Bleeding: If women who have had a hysterectomy develop vaginal bleeding, the consulting gynecologist should be unblinded and appropriate management instituted. The participant is not unblinded. Topical estrogen is acceptable management for atrophic vaginitis so long as it is not administered for more than 3 months/year.

For women with uteri, any bleeding occurring 6 months or later after randomization or heavy bleeding occurring within the first 6 months, should trigger unblinding of the consulting gynecologist and an endometrial biopsy.

- If a woman is on Prempro and the biopsy shows normal, atrophic, proliferative, secretory or insufficient results, the consulting gynecologist may reassure the participant and offer her a choice of *1)* continuing on her current regimen of study pills, or *2)* administering a course of additional progesterone to suppress endometrial proliferation. Efficacy of the extra progesterone should be assessed, and it may be continued if necessary.

If the biopsy shows hyperplasia, a 3 month course of medroxyprogesterone 20 mg daily or megace should be administered, and the endometrial biopsy repeated. If simple hyperplasia persists, re-treatment with MPA 30 mg/day may be appropriate. If, however, hyperplasia has progressed to complex, the consulting gynecologist should refer the participant back to her primary physician who should decide if further evaluation is warranted.

If the biopsy shows atypia or cancer, study medication should be discontinued and the participant referred back to her primary care provider for further evaluation.

- If a woman is on placebo and the biopsy shows normal, atrophic, proliferative, secretory or insufficient results, the participant may continue on her study medications. If bleeding persists, she should be referred to her primary care provider.

  If the biopsy shows hyperplasia, atypia or cancer, study medication should be discontinued and the participant referred back to her primary care provider for further evaluation.

6.2.3 SIDE EFFECTS OF ANTIOXIDANTS

Vitamins C and E are generally thought to be safe at the doses used in WAVE.

Minor symptoms: Possibly due to HRT study medication, initial management of minor symptoms is palliative. Individuals taking vitamin C may report gastrointestinal upset, dyspepsia or heartburn. Women may try taking their vitamins with meals or increasing water consumption with the study pills. Vitamin E may be associated with nausea, which may also improve when study medication is taken with meals. Because the goal is to provide around-the-clock antioxidant protection, it is preferred that women take one dose of their antioxidant study medications (vitamin C 500mg plus vitamin E 400 IU or their respective placebos) in the morning and the second dose around dinner time. If participants are unwilling or unable to do so, it's preferable to take all the antioxidant study medication at the same time rather than omit the second dose.

Major symptoms: Although unlikely, it is possible that the vitamin E may affect the extent of anticoagulation in women taking warfarin. They should be having periodic evaluation of International Normalized Ratio (INR) by their primary care provider; further, the protocol requires INR determination one month after starting antioxidant study medication in women taking warfarin. Nonetheless, women who develop unexpected bleeding (other than vaginal

bleeding, which may be attributed to the HRT study medication), should be asked to contact their coordinators.

6.2.4 MANAGEMENT OF ABNORMAL LAB RESULTS

During the course of WAVE, a number of study participants may have abnormal results of tests obtained for study purposes. The following information is provided to assist study coordinators and investigators in their discussions with study participants about these abnormal tests.

Abnormal Pap smear: In 1992, the National Cancer Workshop convened to develop guidelines for management of women with abnormal Pap tests reported using the Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses, which attempted to provide uniform diagnostic terminology. The guidelines were directed mainly at low-grade cellular abnormalities, low-grade squamous intraepithelial lesion (LSIL) and atypical squamous cells of uncertain signifigance (ASCUS). These two diagnoses account for 95% of abnormal Pap smears, and their management remains controversial. In general, ASCUS constitutes no more than 5% of Pap smear reports; 25-30% of women with ASCUS have dysplasia. Approaches to management of ASCUS vary depending on women's risk for dysplasia, e.g. prior abnormal Pap smears, exposure to human papilloma virus, number of sexual partners, history of other sexually transmitted diseases. Those considered at high risk are often referred for colposcopy, whereas women at low risk may be followed with frequent Pap smears.

About half the women diagnosed with LSIL, the lowest grade of dysplasia in the Bethesda System, regress spontaneously to normal cytology within 2 years. Low risk women with LSIL may be followed with serial Pap smears. High risk women, or those with more than one abnormal Pap smear are usually referred for colposcopy and directed biopsy.

Women in WAVE with LSIL, atypical glandular cells of uncertain significance (ASCUS), or higher grades of dysplasia should be referred to their gynecologists or primary care physicians for further evaluation and management. None of the WAVE study medications is associated with increased risk of cervical cancer.

Abnormal mammogram: WAVE requires baseline and annual mammograms. Abnormalities such as clustered microcalcifications, masses, or areas of asymmetry and architectural distortion identified on screening mammogram are evaluated with a diagnostic mammogram, which includes additional projections and spot compression and magnification views. The combination of extra views and ultrasound will demonstrate that as many as half of indeterminate abnormalities found on screening mammograms are unequivocally benign or can be followed with interval mammography, and do not require biopsy. Of mammographically-detected abnormalities which are biopsied, 30% are malignant.

Just as for Pap smears, a standardized reporting system, the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS), has been developed for mammograms. Categories 1 and 2 are considered negative and require no further work-up. In categories 3 and 4, the presence of an associated palpable abnormality on physical examination would be an indication for biopsy. In the absence of a palpable abnormality, a 6 month follow up mammogram is indicated for category 3 findings. Category 4 represents an indeterminate abnormality, and biopsy should be strongly considered. A category 5 lesion is highly suspicious for malignancy, and biopsy is indicated.

HRT has been associated with an increased likelihood of being diagnosed with breast cancer, although with a reduced risk of death from breast cancer. Therefore, a conservative approach to mammographic abnormalities is warranted in WAVE.

- With regard to eligibility at baseline, categories 1 and 2 are eligible, categories 4 and 5 are not unless biopsy has confirmed the non-malignant nature of the mammographic abnormality. Eligibility of women with category 3 abnormalities is at the discretion of the study investigator.
- During follow up, HRT study medication for women with abnormal screening mammograms may be continued if it is anticipated that evaluation of the mammographic abnormality will be completed within 30 days. If evaluation is expected to take longer, or does take longer, HRT study medication should be temporarily discontinued. Complete form W06 and document events in the progress notes. If biopsy remains benign, study medication should be resumed and Form W06 completed again. The participant may continue taking her study medication. If biopsy reveals cancer, study medication should be permanently stopped.

7. PROTOCOL ADHERENCE

7.1 PATIENT ADHERENCE TO THE PROTOCOL

7.1.1 Medication Adherence

Medication adherence will be assessed at each of the semi-annual follow up visit starting at the 6 month visit. The assessment will consist of a pill count for each of the three coded study medications. This count should be reported on the follow up form (W07).

7.1.2 Adherence to Visit Schedule

All attempts should be made to schedule the follow up visits within their appropriate time window. If this is not possible, the visit should be scheduled as close to the window as possible. In particular, if a visit is missed, and the patient is still on study medication, the visit should be re-scheduled in order to re-supply the patient with study medication. Windows for study visits are described in chapters **Error! Reference source not found.** and **Error! Reference source not found.**.

7.2 DOCUMENTING PROTOCOL DEVIATIONS

During the course of any trial protocol deviations may occur. For the WAVE trial, possible protocol deviations are:

- Unmasking of study personnel, whether accidental or intentional.
- The wrong study medication being given.
- Use of open label estrogen, progesterone, or vitamins C or E above RDA by the patient.
- Study personnel prescribing additional HRT, (e.g. medroxyprogesterone or Premarin) for side effects.
- Participant goes off study medication to take open label vitamins or HRT prescribed by a non-WAVE physician.

- Participant takes open label vitamin C or vitamin E on their own in addition to study medications. If participant wants to take open label vitamin C or vitamin E or HRT, they should stop the corresponding study medications.

The items listed above are meant as examples and do not constitute a complete list of protocol violations. All protocol deviations should be reported to the SCC on form W15 as soon as they are discovered. All protocol deviations will be periodically reviewed by the DSMB.

7.3 UNBLINDING PROCEDURE

In WAVE, there are no situations in which unblinding is required by protocol. As a rule, management of minor symptoms and bleeding can proceed without knowledge of treatment assignment. If a participant develops a major adverse event, such as deep venous thrombosis, breast or endometrial cancer, study medication will be permanently discontinued regardless of treatment assignment. Nonetheless, if an occasion arises in which unblinding is essential, the investigator should contact the SCC.

7.4 SITUATIONS THAT MAY REQUIRE TEMPORARY OR PERMANENT DISCONTINUATION OF STUDY MEDICATION

The following situations may require temporary discontinuation of study medication:

- Any hospitalization
- Accidents or health conditions resulting in immobilization, e.g. hip fracture, stroke - HRT study medication should be stopped temporarily because of the enhanced risk of deep venous thrombosis associated with HRT. Study medication may be resumed once the participant is active again.
- If a woman is prescribed open label HRT by her private physician, HRT study medication must be discontinued for as long as she remains on the open label HRT. She should continue on her antioxidant study medications.
- If a participant takes supplemental vitamin E above the RDA, either on the recommendation of her physician or on her own, her vitamin E study medication should be discontinued for as long as she remains on the open label vitamin E. She should continue on her HRT and vitamin C study medications. If a participant takes supplemental vitamin C above the RDA, either on the recommendation of her physician or on her own, she may continue on her WAVE study medication.
- Triglycerides above 1000 mg/dl - HRT study medication may be temporarily discontinued until hypertriglyceridemia has been controlled. Study medication may be resumed at the discretion of the clinic physician.
- Any severe illness during which administration of study medications is inappropriate.

If a participant needs to temporarily discontinue her study medications, complete form W06. Maintain contact with the participant and her physician to determine if and when she should resume study medication. Complete form W06 again when study medication is restarted.

8. ASCERTAINMENT AND DOCUMENTATION OF OUTCOMES

8.1 WAVE Outcomes

WAVE outcomes are health events or related medical procedures that have been chosen by WAVE investigators as being of study interest. The primary outcome for WAVE is angiographic. Secondary outcomes include both angiographic and clinical endpoints. Outcome data are to be ascertained in an unbiased, accurate and expedient manner. Ascertainment procedures for clinical outcomes include the identification, investigation and documentation of WAVE outcomes relevant to both safety and potential efficacy of the study interventions. The ascertainment process should be completed within 30 days of identification of possible clinical outcomes.

8.1 OUTCOMES REQUIRING DOCUMENTATION

The following outcomes must be documented:

- deaths
- breast cancer
- endometrial carcinoma and hyperplasia
- pulmonary embolism, deep venous thrombosis
- symptomatic gall bladder disease
- major bleeding (defined as bleeding requiring transfusion), not associated with surgery or a revascularization procedure

Collection of outcome data is also required for the following additional diagnoses relevant to the efficacy of the interventions:

- hospitalization for cardiovascular event, including (but not limited to) cardiogenic shock, cardiac arrest, acute myocardial infarction, cardiac tamponade, congestive heart failure, unstable angina, stroke, transient ischemic attack, or arrhythmia
- coronary, carotid or peripheral angiography or revascularization

To ensure that outcomes of interest are not missed, a face sheet with ICD-CM codes (see Apppendix B) is requested for every overnight hospitalization.

8.2 DOCUMENTATION OF OUTCOMES

Potential outcomes may be identified during any patient contact, and should be recorded on either the Follow Up Form (W07) or the Gynecological Follow Up Form (W08) which is transmitted to the SCC. A single W09 form is require for

- All events or procedures that occur during a single hospitalization (i.e. after the patient is admitted, and before she is discharged)
- All events or procedures that occur on the same day

Events that occur in different hospitalizations should be reported on separate W09 forms. Some events may occur outside a hospital admission. This includes events in the emergency room, outpatient procedures, tests obtained in clinics or events occurring at home. Such events are reported on the same W09 if they occur on the same day, but on separate W09s if they occur on different days.

Documents supporting outcomes should be obtained, appended to their corresponding Outcomes Form, and forwarded to the SCC within 30 days of identifying an outcome. One copy of supporting documents should be stored in the participant's clinic file. **Patients should be identified by their randomization number only.** Any identifying information such as patient's name or hospital number must be removed from the copies sent to the SCC.

8.2.1 DEATH

Upon discovery of the death of a study participant, initiate the Outcomes Form and promptly notify the SCC of the death by telephone. Required documentation for death includes the following:

- a copy of the official death certificate;
- if the participant was hospitalized, a copy of the
    a. hospital face sheet with ICD-CM codes and
    b. discharge summary
- if the participant was not hospitalized and an ambulance was called, the emergency medical services report;
- if an autopsy was performed, a copy of the autopsy report;
- a narrative summary of events prior to the death prepared by the PI and any other relevant data.

8.2.2 BREAST OR ENDOMETRIAL CANCER OR HYPERPLASIA

Upon discovery of breast, endometrial cancer or endometrial hyperplasia, complete the Outcomes Form and provide the following documentation:

- dated pathology report documenting the diagnosis;
- if hospitalized, a copy of the
    a. hospital face sheet with ICD-CM codes and
    b. discharge summary

8.2.3 PULMONARY EMBOLISM, DEEP VENOUS THROMBOSIS OR SYMPTOMATIC GALL BLADDER DISEASE

Upon discovery of pulmonary embolism, deep venous thrombosis or symptomatic gall bladder disease, complete the Outcomes Form and provide the following documentation:

- dated report of diagnostic test identifying pulmonary embolism (lung scan or pulmonary arteriogram), deep venous thrombosis (Duplex scan, plethysmography, or venogram), or gall bladder disease (ultrasound or CT or Hida scan); note that asymptomatic gallstones is not an outcome;
- if hospitalized, a copy of the
    a. hospital face sheet with ICD-CM codes and
    b. discharge summary

8.2.4 MAJOR BLEEDING

The combination of estrogen with vitamin E may increase bleeding risk in women taking other anticoagulants or anti-platelet agents. Major bleeding, that is, hemorrhage requiring red cell transfusion, will be documented as an outcome as this may be of particular concern. If the bleeding occurs in association with a surgical revascularization procedure, it does not require documentation. Required documentation includes:

- if hospitalized, a copy of the
    a. hospital face sheet with ICD-CM codes and
    b. discharge summary
- if not hospitalized, a narrative summary of the circumstances

8.2.5 CARDIOVASCULAR HOSPITALIZATION

Hospitalizations for cardiovascular diagnoses will be documented with a copy of the hospital face sheet including ICD-9 codes and a discharge summary (see Appendix B for ICD-9 codes). Note that transient ischemic attacks or other diagnoses made without hospitalization are not outcomes. Required documentation includes:

- a copy of the
  a. hospital face sheet with ICD-CM codes and
  b. discharge summary
- for hospitalization for acute myocardial infarction, also obtain and append the
  a. cardiac enzyme laboratory report and
  b. initial and last electrocardiograms

8.2.6 ANGIOGRAPHY OR REVASCULARIZATION

Coronary, carotid or peripheral angiography or revascularization (balloon angioplasty, stent, bypass surgery, endarterectomy or other revascularization intervention) with or without hospitalization is an outcome. Required documentation includes:

- for coronary, carotid or peripheral angiography, a copy of the angiography report;
- for coronary, carotid or peripheral revascularization,
  a. a copy of the procedure or operative report and
  b. a face sheet with ICD-CM and CPT codes.

8.2.7 ALL OTHER HOSPITALIZATIONS

Participants may report they were hospitalized for a reason which sounds unrelated to cardiovascular disease. Nonetheless, cardiovascular outcomes may have occurred without the participant's knowledge or recollection. To ensure that cardiovascular outcomes, such as perioperative myocardial infarction during non-cardiovascular surgery are not missed, a copy of the hospital face sheet with ICD-CM codes is required for all overnight hospitalizations. No documentation is required for emergency room visits or outpatient procedures other than angiography or revascularization.

9. HANDLING OF STUDY MEDICATIONS

9.1 GENERAL DESCRIPTION

The WAVE Trial consists of 8 different study medications, blinded in a two by two factorial design. Each of the medications in the four groups will have 215 tablets per bottle. Yearly production is projected to be 1,860 bottles of 215 tablets each for the two groups of Vitamins. The 200 bottles of Premarin 0.625 mg and the 400 bottles of Prempro and matching placebos will be hand labeled by the Drug Distribution Center (DDC). The Vitamin C and E tablets and matching placebos will arrive in bulk and will be bottled separately and labeled.

The following medications will be used in the WAVE trial:

- Premarin 0.625 mg tablets, Active and Placebo tablets
- Prempro (Estrogen 0.625 mg plus Medroxyprogesterone 2.5 mg tablets), Active and Placebo tablets
- Vitamin E capsules, Active and Placebo capsules (400 IU)
- Vitamin C tablets, Active and Placebo tablets (500mg)

- Cycrin 2.5mg, 100 tablet bottles (open label)
- Cycrin 10 mg, 100 tablet bottles (open label)
- Premarin 0.3 mg, 100 tablet bottles (open label)
- Centrum Silver, 100 tablet bottles (open label)

9.2 SHELF LIFE

The shelf life for all WAVE trial products should be a minimum of 24 months after delivery to the DDC. This factor will have a major impact on the time line for the manufacturing, packaging and distribution of the drugs.

9.3 BULK DRUG WAREHOUSING

All WAVE trial medication will be donated by the manufacturers and shipped to the DDC at no cost to the DDC. When bulk study medication and antioxidants are received at the DDC, they will be inspected and then stored in the same manufacturer's bulk containers until ready for repackaging. The HRT medications will arrive pre-bottled.

9.4 BOTTLING

The DDC will be responsible for the bottling (active and placebo study vitamins only), labeling, storage, and distribution of all WAVE trial medications in strict compliance with current FDA Good Manufacturing Practices Regulations.

Note: The Premarin and Prempro study medication that will be received already packaged from Wyeth-Ayerst in a rectangular bottle, which will not allow the use of automated labeling machines for label application. All Premarin and Prempro study drug will need to be hand labeled and strict FDA and Quality Standards will be followed to prevent labeling errors.

9.4.1 OPEN LABELED STUDY DRUG

The open labeled Medications will be received at the DDC already bottled and labeled. They will be warehoused, inventoried, pulled and shipped to WAVE clinics as needed. The DDC will distribute open labeled Cycrin tablets 2.5 mg and 10 mg, 100s and open Premarin tablets 0.3 mg, 100's and labeled Centrum Silver tablets 100s to all 5 clinics, on an as needed basis.

9.4.2 LABEL FORMAT

The study drug label will be similar to that proposed by the DDC (see below). The study drug labels will indicate the name of the study, code number, dosage instructions, control number, storage instructions, expiration date, number of tablets in the bottle and any other information required by law.

WOMEN'S ANGIOGRAPHIC VITAMIN AND ESTROGEN TRIAL
CODE C-01 WAVE

Directions: Take one (1) tablet twice a day as directed.
Note: Return unused medication to your WAVE Trial Coordinator.
CAUTION: NEW DRUG - Limited by Federal (USA) Law to Investigational Use.

Store at room temperature away from direct sunlight or heat.

WARNING: KEEP OUT OF THE REACH OF CHILDREN
Packaged By: HHS Supply Service Center, Perry Point, MD 21902
LOT NUMBER: 12345 EXP. DATE: 05/99 215 TABLETS

9.4.3 CODE NUMBER ON LABELS

The WAVE Statistical Coordinating Center will provide the DDC with a list indicating the code number assignments for the 8 different study medications. The four medication treatment groups will be double-blinded to prevent all participants, as well as clinic staff, from knowing if they are on active or placebo medication.

9.5 DISTRIBUTION

The WAVE Statistical Coordinating Center will develop an ordering form for the clinics to use when requesting drugs. All requests for coded study medication (HRT and vitamins) should be sent to the SCC, not to the drug distribution center. This is necessary, especially during the initial phase of the study because the randomization lists are kept at the SCC and the drug distribution center will not know what kits are needed to cover the next several randomizations. Orders for open label medication should be sent to the DDC directly. The DDC will process orders from the clinics within 2 days of receipt of the order. The DDC will pull material and pack for shipping by next day Federal Express or equivalent to the requesting sites.

9.6 INVENTORY

The DDC will maintain confidential and current computerized inventory records of all available quantities of trial medication and provide reports when requested by the SCC. These reports will occur at least every three months. Local inventory will be the responsibility of the WAVE trial coordinator. The SCC will monitor local supplies based on the data from the study forms. In addition, the WAVE trial coordinators will be asked to conduct a complete inventory of study drugs stored locally every 3 months and report the results to the SCC.

9.7 REPORTS

The DDC will maintain confidential and current computerized records of all orders processed for each clinical center. This report will give dates and quantities of drug issued to each clinic.

9.8 EMERGENCY SUPPLY

The study drug requirements of each clinic can usually be predicted fairly accurately by considering when the patients were randomized and when they are due for their semi-annual

visits. Occasionally, however, a clinic may have an unexpected need for study drug, for example if a visit is scheduled unusually early, or if the patient has lost her pills and needs a re-supply.

To ensure that the clinics have adequate supplies of study drug to meet unexpected needs, an emergency box will be provided to each clinic. This box will contain a full dose of each of the 52 drug codes in use in the study. This emergency supply should be kept separate from the regular drug supply. **If a clinic needs to pull bottles from the emergency supply, the SCC should be notified immediately**.

10. CORE ANGIOGRAPHIC LABORATORY

10.1 BACKGROUND

10.1.1 QUANTITATION METHODS AND VALIDATION AT STANFORD

The coronary arteriographic quantitation system at Stanford was developed by Mr. William Sanders and initially reported in 1979 (Sanders 1979, Alderman 1981, Sanders 1988). The system hardware and programs have had several iterations, with addition of multiple features. The system features related to image digitization include:

- Dual cine digitizers for simultaneous viewing and analysis of angiogram pairs
- 1300 x 1030 pixel CCD digitizer for analysis
- Approximately twenty pixels per mm at average magnification.
- Automatic optimization of image brightness and contrast to minimize operator bias
- Electronic zoom and pan for rapid region of interest selection
- Capability for cine, CD or combination for analysis
- Integrated database, data backup and data transfer capability

The quantitation algorithms have been validated using lucite phantoms containing nine cylindrical holes ranging from 0.5 to 4.53 mm (Leung 1991). The phantoms were filled with radiographic contrast and filmed on a torso phantom under standard radiographic parameters associated with coronary arteriography. The average difference between measured and true diameters under varying conditions ranged from 0.047 to 0.085 mm (mean 0.069mm) with a mean pooled standard deviation of the differences (precision) of 0.066. The correlation of intraobserver frame to frame reproducibility of minimum diameter was 0.973 with an average difference of 0.041 mm (SD: 0.052). Interobserver frame to frame measurements yielded an r of 0.961, a mean difference of 0.053 mm and a SD of 0.064.

10.2 CONSIDERATIONS RELEVANT TO QUANTITATIVE ARTERIOGRAPHY

10.2.1 OVERALL TRIAL DESIGN

The WAVE trial will recruit 450 women randomized (2 by 2 design) into four treatment groups at 5 clinical sites. Lesions >15% severity will be quantitated for change in minimum lesion diameter (MLD) from entry to follow-up exit arteriography three years later.

10.2.2 CLINICAL SITE CHARACTERISTICS RELEVANT TO ARTERIOGRAPHY

In order to optimize arteriographic image acquisition, the angiographic equipment, operators, and logistics must be considered. The following is brief survey of the imaging capability, patient flow and logistics at each of the WAVE clinical sites.

University of Alabama
Principal Investigator: William Rogers, M.D.
Cath Angio Laboratory Director: Larry Dean, M.D.
Technical Director: Dale Corr, M.D.

At the University of Alabama, most patients for the WAVE Trial will be recruited through the University Hospital Laboratories. Some patients may have entry arteriograms at the adjacent Kirkland Outpatient Catheterization Laboratory. There are a total of five procedure rooms applicable to this study, four Phillips rooms at the University hospital and one Philips room at the Kirkland Clinic. The Kirkland Clinic room is digital only, without cine capability. All four University laboratories have cine capability, although cine is used infrequently because of cost and logistic complexities. At the present time, the cine film is being used less and less, requiring special extra effort in order to have cine films appropriately processed. Images are acquired by the Philips equipment at 1,000 + horizontal and vertical pixel resolution and with images recorded on analog optical disks for replay. There are plans to convert to DICOM standard CD-R format, however conversion costs are substantial.

Johns Hopkins University
Principal Investigator: Pamela Ouyang, M.D.
Cath Angio Laboratory Investigator for WAVE Trial: Thomas Aversano, M.D.

Johns Hopkins will be recruiting patients through the University hospital catheterization laboratory and also at Bayview Medical Center where Dr. Bush is the collaborating investigator. There are four procedure rooms, one Siemens biplane, and three G.E.. All rooms are cine for now, but most likely some will have digital Flu. It is anticipated that most WAVE Trial patients will be recruited at the time of their entry arteriogram with prior identification of suitable candidates. It is anticipated that candidates will be identified in advance in order that appropriate measures be taken during imaging for optimal subsequent quantitation.

Hartford Hospital
Principal Investigator: David Waters, M.D.
Cath/Angio Project Director: Fran Kiernan, M.D.

It is anticipated that most patients will enter the study as a result of a clinically indicated angiogram performed because of chest pain or other manifestations or coronary disease. It is planned that all procedures on women who are potential candidates for the WAVE Trial will be done in a manner that will permit subsequent quantitation. There will be four procedure rooms applicable to the WAVE Trial; two Philips and two Trex. All have cine capability and it is anticipated that at least one room will continue to have cine capability for the purposes of follow-up arteriograms for the duration of the WAVE Trial. The angiographic procedures will be performed by any one of seven angiographers within this closed access laboratory. A member of the investigative staff will screen all the potential cath patients for WAVE Trial candidates.

Washington Hospital Center
P.I. Barbara Howard, Ph.D.

A majority of patients entering the study at Washington Hospital Center will have had prior angiography and are referred for interventional procedures. Therefore, it will be possible to identify female subjects who meet the clinical and angiographic criteria and thus will have their

arteriograms performed in a manner suitable for quantitation. Moreover, there are two female co-investigators who are invasive cardiologists, Dr. Alexandra Lansky and Dr. Lucy VanVorrhes. All of the angiograms will be performed at Washington Hospital Center, however there are seven procedure rooms. At the present time, cine film is available in all rooms, but it is anticipated that there will be a changeover to digital on a gradual basis over the coming years.

Duke University
PI: Frederick Cobb, M.D.

The director of the Catheterization Laboratory is Mike Sketch, M.D. There are six procedure rooms applicable to this study, all of which are Phillips rooms with digital capability. Some of the older rooms have the DCI system, but most are the newer Intregras systems with dual track CD-M capability. The lab will be cineless for the purposes of the WAVE trial. The investigators plan to identifying all female patients coming through the Cath Lab who are post-menopausal and are potential candidates for the WAVE Trial. The angiography would be done in a manner that would lend itself to subsequent quantitation.

10.3 CLINICAL SITE PROTOCOL FOR ANGIOGRAM ACQUISITION

10.3.1 PATIENT PREPARATION AND PREMEDICATION

Patients should be adequately hydrated prior to the procedure (patients with creatinine >2.0 mg/dL are excluded from protocol). Premedication can include Benadryl and diazepam. Medazolam (Versed) can be used as needed.

10.3.2 PROJECTIONS

A minimum of four projections of the left coronary system and two projections of the right coronary artery will be obtained at the time of the study. The angiographer should select additional projections that optimize visualization of all portions of the coronary anatomy. Additional projections are encouraged because this increases options to overcome glitches in one view on either entry or concluding angiograms and maximizes the chances to obtain optimal matches of the entry and concluding angiograms. Use collimators to minimize burnout. Cineangiographic projection angles used in the baseline arteriography must be noted and replicated on subsequent angiograms.

Recommended projections for the LCA are:

- Cranial 15-25 degrees, steep LAO (70-80 degrees)
- RAO 20-30 degrees; Caudal 15-25 degrees
- Cranial AP (particularly for the LAD)
- Shallow LAO or AP (If patient is slender; for left main and proximal LAD and Circ) Lateral

Recommended views of the RCA are:

- 30-45 degrees RAO
- 45-60 degrees LAO
- Cranial LAO

10.3.3 NITROGLYCERINE ADMINISTRATION

Nitroglycerin (150 μgm) must be given ic into both the right and left coronary arteries prior to arteriograms of each vessel. Wait at least 45 seconds before coronary angiographic recordings in

order to maximize vasodilitation and to enhance visualization. Arterial pressure should be checked prior to NTG administration. Give ic NTG even if patient has a NTG patch on, or has had recent po dose of nitrates. If the patient has NTG paste on, wipe it off before starting the angiographic procedure and give IC NTG. In general, ic NTG in the specified doses will not cause hypotension or headaches. A cine marker on the angiogram indicating NTG is preferred. (e.g. ic NTG).

10.3.4 CORONARY ARTERIOGRAPHIC RECORDING

Recordings, in general, should be made using mid magnification, however in slender women of small stature, greater magnification is preferred. At least 5 cm of the distal portion of the catheter must be visualized with each of the coronary injections. Panning across the plane of the imaging plane is acceptable, but should be minimized particularly in marked cranial or caudal projections. Panning in a direction perpendicular to the imaging plane must be avoided. Center the catheter image and the main portion of the coronary vessels within the image field. Record cines at 25-30 fps.

Post-PTCA recording-Record at least two orthogonal projections of dilated lesion, matching baseline projections, after guidewire removed and post additional ic NTG.

10.3.5 CATHETER CALIBRATION

The diameters of contrast filled catheters provide scaling factors for measuring luminal diameters. If a 5 Fr. catheter was used, it will be necessary to upsize to larger catheters.

Each clinical site will note the size and type of catheters used for each coronary injection on the Angiographic Procedure Form. It is preferable that the same catheter (manufacturer, type and size) be used consistently for all procedures in the same patient. The contrast filled catheter will be imaged on a radiographic system at the core laboratory against a radio-opaque grid to calibrate a scaling factor for each catheter.

10.3.6 RADIOGRAPHIC IMAGING SYSTEM USED (PROCEDURE ROOM)

Every effort should be made to perform follow-up angiograms in the same procedure room used at baseline.

10.3.7 SYSTEM CALIBRATION

Each clinical site laboratory will be required to image a rectangular grid in the procedure rooms planned for these studies in order to assess pincushion distortion. (This is to be done at the pre-enrollment site visit and again if major changes in the imaging chain are made.)

10.3.8 CONTRAST

Non-ionic contrast is preferred. However, if a different contrast is used then it must be noted and the same contrast used on the follow-up study. Note on the angiographic procedure form which type of contrast is used.

10.3.9 SEQUENCE OF PROCEDURES:

If coronary ultrasound is being performed, it must follow diagnostic arteriography. LV angiography, in general, should follow the coronary arteriogram, although not mandatory.

10.3.10 DATA FORM COMPLETION

Data forms are self explanatory. Samples of completed forms are included. Please note the times of IC NTG administration as noted on the form.

Two parallel logs of angiogram status will be maintained at the Central Angiographic Lab (CAL): a paper log and a computer filmlog database. These will both identify the site and patient ID#, the procedure date of the angiogram, the date the angiogram arrived at the CAL, the date it was sent for film duplication and the date of return to the CAL, the date analyzed and the date the angio is returned to the clinical site.

10.3.11 CONFIDENTIALITY: CINE FILM

Overtaping of nameplate and date information

In lab angio quality review
Catheter calibration
Nitroglycerine administration
Adequate visualization of: Qualifying lesions and coronary vasculature
Avoid burnout and out of plane panning
Data form completion
Follow-up angiograms
For follow-up visits angio review against prints of entry angiogram

10.3.12 IN-LAB IMMEDIATE ARTERIOGRAPHIC QUALITY REVIEW

As each cine run is performed it is scanned for the following items. If deficient, the recording is repeated. The distal portion of the calibration catheter (5-10 cm) encompassing the non tapered portion of the catheter must be within view. Major coronary vessels must be well imaged and no large portions `burned out'. Adequate contrast must be delivered to fully opacify the vessel for one or two complete cardiac cycles. Imaging of catheters or major vessels at the extreme edges of the imaging field should be avoided.

10.3.13 WAVE STAFF MEMBER PRESENT AT ARTERIOGRAMS

The burden of the technical recommendations are such that a knowledgeable study staff member (nurse or technician) must be present at the time exit arteriograms are being obtained. This is also preferable at the time of entry arteriograms, although logistically more difficult. It is recognized that this places a staff member on beeper call to the cath lab when an arteriogram is being performed on any patient who is a likely candidate for WAVE. However, for entry arteriograms, having a WAVE study technician present assures that ancillary information is obtained at the time the arteriogram is performed. These responsibilities can be subsumed by a dedicated cath lab nurse or technician who is trained in the required procedures.

10.3.14 CINE FILM TRANSFER

Angiograms will be transferred to the angiographic core laboratory by secure (traceable) express mail using a two day economy rate. A packing slip will accompany each shipment listing the angiograms included in the package referencing the patient study number, the procedure date, and the study type (entry or exit). A similar packing slip will be used to return the film copies to the clinical sites. Angiogram copies of randomized patients will also be returned using secure express mail using a two day economy rate unless the CAL is notified that a film is needed back immediately, in which case the film will be sent priority.

Each angiogram will be identified with an attached label indicating it as a WAVE study angiogram. The label will be completed to include the patient study number, and procedure date. Each angiogram shipped will be accompanied by two forms, an angiographic procedural report form and a supplemental information form.

10.3.15 RECORDING MEDIA

Catheterization laboratory imaging is in the midst of a gradual conversion to digital (filmless) image acquisition. The new DICOM Digital Interchange Standard for Cardiology (DISC) provides a means for recording images on digital CD-ROM discs that are easily readable by other institutions.

Cine film has detail approaching 4000 x 4000 pixels, although this resolution is not realized in cine angiography. Current x-ray imaging systems acquire digital images with a resolution of at least 1000 x 1000 pixels. However, the DICOM DISC standard is currently designed for only 512 x 512 pixels. The potential resolution of cine angiography probably surpasses 512 x 512 pixels. Therefore, the accuracy of QCA from 512 x 512 images may be less than from cine film. It is hoped that current efforts to add higher resolution (e.g., 1024 x 1024) to the DICOM standard will result in higher resolution images being available by the time follow-up arteriography. Because QCA Plus is already able to process 1024 x 1024 images and because we have developed our own software to read and analyze DICOM discs, we shall be able to quickly implement the capability to perform QCA from discs with higher resolution images.

Hartford Hospital, Johns Hopkins Hospital and Washington Hospital Center, plan to retain cine film capability for the duration of the WAVE trial. Duke and the outreach cath lab associated with Johns Hopkins have limited or non-existent cine capability and will use CD-ROM recordings to transfer angiography to the core laboratory. Alabama will use cine film or possibly current video disc format for image transfer to Stanford with plans to convert to DICOM CD in the future.

Stanford will process cine film and DICOM discs in any combination, however, either cine film or "hi resolution" 1024 x 1024 CD-ROM images, are preferred. The 512 x 512 format is adequate for this study. We continue to communicate with radiographic equipment companies and image storage companies (Camtronics, Eigen) and will advise clinical center investigators about type and availability of DICOM standard technologies as they emerge. The 512 x 512 format is a reasonable compromise and endorse upgrade to the hi-res DICOM format as soon as possible. We will not process video tape for coronary quantitation.

11. CENTRAL BIOCHEMISTRY LAB

11.1 INTRODUCTION

The Central Biochemistry Laboratory (CBL) will participate actively in the study, interacting with the Clinical Centers. Since this study will last several years, the continuity of the laboratory in assuring quality analyses and the preservation of specimens remains its most important contribution in response to the work outline in the RFP. Although this summary primarily addresses technical issues, the quality of the specimens (and ultimately the results generated if and when the analyses will be performed) rests upon excellence in following the protocols established by the WAVE Study Group.

11.2 PREPARATION

11.2.1 PARTICIPANT CONTACT

Since the study depends on the voluntary participation of participants, every effort must be made to make the entire procedure as easy and painless as possible for them. The technicians must 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 for the technicians to be thoroughly

knowledgeable about all aspects of the procedures. The WAVE study involves the collection of 14 - 48 mL of blood from each participant, depending upon the visit. Two to seven tubes of blood are collected. Any participant who is concerned about the volume of blood should be reassured that the total amount of blood drawn is less than two ounces although it may look like more. The technician may also assure participants that they donate ten times as much blood (450 mL) when they donate a pint of blood.

11.2.2 BLOOD COLLECTING TRAYS AND TUBES

Prior to venipuncture prepare two trays for each participant. One tray holds the tubes used in the blood collection. The other tray holds the various plastic vials which contain the final serum and plasma aliquots which are to be processed and sent to the Central Laboratory for analysis. Label these sets of tubes with the laboratory ID number as described in sections 11.2.3 and 11.2.4.

11.2.2.1 Blood Collection Tray

First, the technician organizes and prepares the blood collection tray. The tray itself should be made of hard plastic which is unbreakable and can be easily cleaned. The tray has individual compartments which are filled with the following supplies:

- A test tube rack to hold the blood collection tubes which are drawn from each participant. These tubes are described in detail in the next section.
- Sterile, disposable 21 gauge butterfly needles.
- A plastic tube guide.
- Luer adapters.
- Sterile alcohol swabs.
- Gauze sponges.
- A tourniquet.
- Bandages ("Band Aids").
- Smelling salts, ice packs, and wash cloths should be readily available in the specimen collection area for patients who become faint during the blood draw.

11.2.2.2 Blood Collection Tubes

The volume and type of blood collected from each participant will vary depending upon which visit is taking place. It is important that the technicians know the sequence of tube collection for each visit type. Some visits will not require the collection of all tube types. The tube types are summarized below:

10 mL red and gray-stoppered tube filled with 9.5 mL of blood. The serum from this tube is used for lipid, endocrine and vitamin studies. This tube contains a clotting agent which is activated by mixing following collection. After tipping the filled tube four times, the blood is allowed to clot at room temperature for 30 minutes. The tube is then centrifuged and the serum processed as described later.

4.5 mL blue-stoppered tube containing the liquid anticoagulant sodium citrate. The plasma from this tube is used for coagulation studies. After this tube is filled with blood, invert four times then place into a room temperature rack until centrifugation.

5 mL lavender-stoppered tube containing the liquid anticoagulant EDTA. The plasma from this tube is used for homocysteine and vitamin studies. At the baseline visit, 18 months and 36 months, this tube must be wrapped in tinfoil to protect it from light and placed in ice water immediately after collection. If an additional tube is collected at a given visit, it is simply inverted four times after filling, then placed into a room temperature rack until centrifugation.

10 mL lavender-stoppered tube containing the liquid anticoagulant EDTA. The plasma from this tube is used for lipid analysis and long term storage. After each tube is filled with blood, invert four times then place into a room temperature rack until centrifugation.

5 µL lavender-stoppered conical Sample Preparation vial containing 1 mL of an aqueous solution of EDTA and potassium cyanide (0.25 mmol/L). The hemolysate from this tube is used for hemoglobin A1c analysis. After each 5 µL capillary is filled with blood and placed into the conical dilution tube, cap and shake it to rinse the blood completely from the capillary. Place into a rack and refrigerate until shipment.

Each WAVE visit utilizes a different combination and collection sequence of these tube types:

Baseline:
1. 10 mL red and gray-stoppered tube
2. 10 mL red and gray-stoppered tube
3. 4.5 mL blue-stoppered tube
4. 4.5 mL blue-stoppered tube
5. 5 mL lavender-stoppered tube (light-protected, ice)
6. 10 mL lavender-stoppered tube
7. 10 mL lavender-stoppered tube
8. 5 µL capillary tube in 1 mL lavender-capped Sample Prep vial

3 month:
1. 4.5 mL blue-stoppered tube
2. 5 mL lavender-stoppered tube

18 month:
1. 10 mL red and gray-stoppered tube
2. 4.5 mL blue-stoppered tube
3. 5 mL lavender-stoppered tube (light-protected, ice)
4. 5 mL lavender-stoppered tube

36 month:
1. 10 mL red and gray-stoppered tube
2. 10 mL lavender-stoppered tube
3. 5 mL lavender-stoppered tube (light-protected, ice)
4. 5 µL capillary tube in 1 mL lavender-capped Sample Prep vial

If there arises a case where it is uncertain that the entire specimen set can be collected (e.g. obviously poor veins), the following priority collection sequence should be followed.

1. 10 mL lavender-stoppered tube
2. 10 mL red and gray-stoppered tube
3. 4.5 mL blue-stoppered tube
4. 5 mL lavender-stoppered tube (light-protected, ice)
5. 10 mL lavender-stoppered tube
6. 10 mL red and gray-stoppered tube
7. 4.5 mL blue-stoppered tube
8. 5 µL capillary tube in 1 mL lavender-capped Sample Prep vial

If indicated for a particular visit, the Sample Prep vial should always be filled and processed regardless of the number of tubes successfully completed.

11.2.3 BLOOD COLLECTION TUBES: LABELING AND SET-UP

Attach pre-numbered adhesive laboratory ID labels to each blood collection tube prior to blood collection. Place the labels on the tubes vertically. Arrange the set of tubes in a test tube rack in the order they will be collected. When the participant arrives for the Clinical Center visit, place

laboratory ID label on the Venipuncture form along with the participant's WAVE ID number. Handle only one participant's specimens at a time so the chance of mislabeling is minimized.

11.2.4 SAMPLE ALIQUOT TUBES: LABELING AND SET-UP

Attach pre-numbered adhesive laboratory ID labels to each set of sample storage vials prior to blood collection. The ID labels will match the corresponding set of blood collection tubes. The number of storage vials to be labeled will depend upon the visit type (see section 11.2.2.2). Each type of serum/plasma storage vial has a corresponding color-coded screw cap that fits onto it.

11.2.4.1 Sample Tray

The rack should be a flexible sponge test tube rack which will fit tubes from 10-16 mm in diameter. Other types of racks are also acceptable.

11.2.4.2 Organization

The specimen storage supplies are as follows:

2.0 mL polypropylene microvials
2.0 mL amber glass vials with caps
Red screw caps for microvials
Blue screw caps for microvials
Purple screw caps for microvials
1 mL Sample Preparation vials

Each visit will not require usage of all of the storage supplies. The supplies needed for each visit are as follows:

Baseline:	23 - 2 mL polypropylene microvials
	2 - 2 mL amber glass vials with caps
	10 - Red screw caps for microvials
	4 - Blue screw caps for microvials
	9 - Purple screw caps for microvials
	1 - 1 mL Sample Prep vial for HbA1c
3 month:	2 - 2 mL polypropylene microvials
	1 - Blue screw cap for microvials
	1 - Purple screw cap for microvial
18 month:	11 - 2 mL polypropylene microvials
	2 - 2 mL amber glass vials with caps
	5 - Red screw caps for microvials
	1 - Blue screw caps for microvials
	5 - Purple screw caps for microvials
36 month:	16 - 20 mL polypropylene microvials
	2 - 2 mL amber glass vials with septa and seal
	8 - Red screw caps for microvials
	5 - Purple screw caps for microvials
	1 - 1mL sample prep vial for HbA1c

A rack containing all of the necessary storage vials should be set up prior to blood collection from the WAVE participant. The different types of screw caps should be available in bins in the processing area.

11.3 VENIPUNCTURE

11.3.1 PRECAUTIONS FOR HANDLING BLOOD SPECIMENS

Handle all specimens as potentially infectious for laboratory workers. OSHA rules mandate that technicians must always wear disposable protective gloves when collecting and processing specimens.

Use 0.5% sodium hypochlorite (household bleach diluted 1:10) to clean up any spills of blood, plasma, or serum.

OSHA regulations require that all needles and sharp instruments be discarded into puncture resistant containers.

Avoid formation of potentially infectious aerosols when removing the rubber stoppers from Vacutainer tubes. In addition to wearing protective gloves, hold a piece of gauze over the stopper while slowly removing it from the tube.

Place all used blood tubes and blood-contaminated products in biohazard bags for proper disposal.

11.3.2 PHLEBOTOMY ROOM

The blood drawing takes place in an isolated room or where participants are separated by room dividers.

11.3.3 PARTICIPANT PREPARATION

Informed consent must be obtained before drawing blood. This procedure is followed to ensure that the participants understand the purpose of blood drawing and the possible complications of venipuncture. A standard informed consent will be prepared for this study. With regard to laboratory procedures, the consent statement informs study participants that although there may be some minor discomfort, their blood (about two ounces) will be drawn by trained personnel.

Blood drawing is standardized to the sitting position. It is difficult to standardize the length of time that a person is in the sitting position prior to venipuncture, but allow enough time for the participant to relax before the venipuncture takes place.

Give the participant enough time to feel comfortable after the blood collection, as well. In many cases the most memorable part of the experience for participants will be the contact with the personnel who draw the blood and their general attitude and competence.

11.3.4 VENIPUNCTURE

Before applying the tourniquet, screw the Luer adapter into the plastic tube guide. Insert the butterfly tubing onto the adapter.

With jacket or sweater removed, have the participant sit upright with the sleeves rolled up to expose the antecubital fossa (inner aspect of elbow). The preferred arm to draw from is the left arm. The right arm should be used only if blood collection is not possible from the left arm. This does not mean you must stick the left arm. Only do so if an adequate vein is apparent.

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 two (2) minutes. To do so may result in hemoconcentration or a variation in blood test values. If a tourniquet must be applied for preliminary vein selection, and it remains on the arm for longer than two minutes, it

should be released and reapplied after a wait of two minutes. Instruct the participant that he/she should not clench their fist prior to the venipuncture. Doing so could cause fluctuations in the results in several of the possible analytes to be measured. 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. Wrap the tourniquet around the arm 3 to 4 inches (7.5 to 10.0 cm) above the venipuncture site.

Identify the vein, then cleanse the venipuncture site.

1. Remove alcohol prep from its sterile package.
2. Cleanse the vein site with the alcohol prep using a circular motion from the center to the periphery.
3. Allow the area to dry to prevent possible hemolysis of the specimen and a burning sensation to the patient when the venipuncture is performed.
4. If venipuncture becomes difficult, the vein may need to be touched again with your hand. If this happens, cleanse the site again with alcohol.

Perform venipuncture.

1. Grasp the participant's arm firmly, using your thumb to draw the skin taut. This anchors the vein. The thumb should be 1 or 2 inches (2.5 or 5.0 cm) below the venipuncture site.
2. With the needle bevel upward, enter the vein in a smooth continuous motion.
3. Make sure the participant's arm is in a flat or downward position while maintaining the tube below the site when the needle is in the vein. It may be helpful to have the participant make a fist with the opposite hand and place it under the elbow for support. DO NOT HAVE THE PARTICIPANT MAKE A FIST IN THE HAND OF THE ARM FROM WHICH BLOOD IS TO BE DRAWN.
4. After seeing the blood enter the tubing of the butterfly, place the first collection tube into the plastic barrel and push it forward until the butt end of the needle punctures the stopper, exposing the full lumen of the needle. The tube should begin filling with blood.
5. Remove the tourniquet after tube #1 fills. Once the draw has started, do not change the position of a tube until it is withdrawn from the needle. A tourniquet may be reapplied during subsequent tubes to spare the participant a restick, but the tourniquet must not be on for more than 2 minutes.
6. Keep a constant, slight forward pressure (in the direction of the adapter) on the end of the tube. This prevents release of the shutoff valve and stopping of blood flow.
7. Fill each blood tube as completely as possible; i.e., until the vacuum is exhausted and blood flow ceases. If a tube fills only partially, remove the tube and attach another without removing needle from vein.
8. When the blood flow into the collection tube ceases, remove the tube from the holder. The shutoff valve covers the point, stopping blood flow until the next tube is inserted (if necessary). Tubes which require mixing should be gently inverted four times immediately following removal of the tube from the adapter then placed then placed into the room temperature rack.

At the conclusion of the blood draw:

1. 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 and its cap into needle box. *DO NOT ATTEMPT TO RECAP NEEDLES!* Have the participant hold the gauze pad firmly for one to two minutes to prevent a hematoma.
2. If blood flow stops before collecting all of the tubes, restick the participant, collecting only the unfilled tubes from the previous attempt. A tourniquet may be applied in this case but

should be released if possible as soon as blood flows into the first EDTA tube. As always, the tourniquet must never be on for longer than two minutes.

Bandaging the arm.

1. Slip the gauze pad down over the site, continuing mild pressure.
2. Apply an adhesive or gauze bandage over the venipuncture site after making sure that blood flow has stopped.

11.3.5 BLOOD MIXING DURING VENIPUNCTURE

To invert tubes, hold the tube horizontal to the floor. Slowly tip the stopper end down while watching the air bubble rise to the butt. Now, lower the butt end slightly while watching the bubble float to the stopper (1st inversion). Invert each tube four times. Four inversions should take 6 to 8 seconds.

11.4 BLOOD COLLECTION AND PROCESSING (BASELINE)

Collection and processing of the various blood samples is divided into 3 stages.
Baseline Collection Supplies:

1. 10 mL red and gray-stoppered tube
2. 10 mL red and gray-stoppered tube
3. 4.5 mL blue-stoppered tube
4. 4.5 mL blue-stoppered tube
5. 5 mL lavender-stoppered tube (light-protected, ice)
6. 10 mL lavender-stoppered tube
7. 10 mL lavender-stoppered tube
8. 5 µL capillary tube in 2 mL lavender stoppered Sample Prep vial

Baseline Storage Supplies:

23 - 2 mL polypropylene microvials
2 - 2 mL amber glass vials with septa and seal
10 - Red screw caps for microvials
4 - Blue screw caps for microvials
9 - Purple screw caps for microvials
1 - 1 mL Sample Prep vial for HbA1c

11.4.1 STAGE ONE: IMMEDIATE PROCESSING

At the conclusion of venipuncture, keep all the tubes at room temperature except tube #5 which is placed into ice water.

Tubes #1 and #2 remain incubating at room temperature for thirty minutes to allow the blood to clot (blood at 4°C clots extremely slowly). Set a timer for 30 minutes as a reminder to centrifuge these tubes.

Immediately after all collection tubes are filled and before tube #1 has begun to clot, remove the stopper from tube #1. With a plastic disposable pipette provided, withdraw a very small amount of blood from tube #1 and place one drop on a square of Parafilm™ provided. Take one 5 µL capillary out of the capillary dispenser and grasp it with the capillary tip holder. Touching the capillary tube to the blood drop, fill the capillary with blood end-to-end, being careful to remove any residual blood drops on the outside of the capillary. Transfer the filled capillary into the Sample Preparation vial. Cap the vial and shake it to rinse the blood completely from the capillary. **It is extremely important that no blood remains in the capillary.** Place in rack in refrigerator. This is tube #8. Replace the stopper on tube#1 and allow to clot for thirty minutes.

Place tubes #3, #4, #5, #6 and #7 into the centrifuge trunions. After balancing the centrifuge, spin these tubes at maximum centrifugal force (not to exceed 3,000 x *g*) for 15 minutes at room temperature.

Wait for centrifuge to come to a complete stop. Remove the tubes from the centrifuge as soon as possible. Proceed to stage 2 processing.

11.4.2 OPERATING THE CENTRIFUGE

Refer to Centrifuge Operating Manual for specific operating and balancing instructions. The revolutions per minute (RPM) associated with a specific *g* rating will vary from centrifuge to centrifuge depending on radius of the centrifuge's rotor. To determine if your centrifuge's maximum speed exceeds 3,000 x *g*, consult the centrifuge's operating manual for the appropriate RPM setting for each centrifuge.

11.4.3 STAGE TWO:

Approximately 15 minutes after venipuncture.

11.4.3.1 Blue-Stoppered Tubes (Tubes #3 And #4)

1. Remove tubes from the centrifuge and place in the test tube rack which contains four sample aliquot tubes labeled with the corresponding participant number. Remove the stoppers.
2. Using a plastic transfer pipette, take only about the top 2/3 of the plasma (the bottom 1/3 of the plasma contains platelets and we want platelet free plasma) and transfer the plasma equally into four 2-mL microsample tubes.
3. Fasten the blue screw caps onto the vials and allow them to remain in the rack.
4. Restopper the sample collection tubes #3 and #4 and discard them in a biohazard waste bag.
5. Leave the rack holding the filled aliquot vials at room temperature until it is time to remove the serum from tube #1 and tube #2.

11.4.3.2 Lavender-stoppered Tubes (Tubes #6 and #7).

1. Remove the tubes from the centrifuge. Remove the stoppers.
2. Using the plastic transfer pipette, and being careful not to disturb the cell layer, remove the clear plasma supernatant from tubes #6 and #7. The pipette tip should not get any closer than one-half inch from the cells. Inspect for hemolysis, then transfer six 0.5 mL aliquots into 2 mL microsample tubes, one 1.0 mL aliquot into a 2 mL microsample tube and two 2.0 mL aliquot into 2 mL microsample tubes. After leaving one-half inch of plasma on the cells, any excess plasma may be added to the tubes. *Do not overfill!*
3. Fasten the purple caps on the sample aliquot tubes and place them in the rack.
4. Replace the stoppers on the lavender top blood collection tube #6 and #7 and discard in a biohazard waste bag.
5. Leave the rack holding the aliquot vials at room temperature until tube #1 and #2 are ready. Remove one 0.5 mL aliquot tube and place it into the refrigerated rack with tube #8. All other aliquot tubes are to remain at room temperature until frozen.

11.4.3.3 Lavender -stoppered Tube (#5 light protected)

1. During centrifugation, volumetrically deliver 1.5 mL Vitamin C preservative (provided by the CBL) into each of two amber colored Wheaten vials. To deliver 1.5 mL, place a disposable plastic tip onto the 500 µL (0.5 mL) MLA pipet. Aspirate the solution and dispense it into a vial. Repeat this step two more times, dispensing into the same vial. Repeat this procedure

with the second vial. Discard the tip. Replace the caps (septa) until ready to pipet the EDTA plasma.

2. Remove the lavender light - protected tube from the centrifuge. Remove the stopper.
3 Place a clean plastic tip onto the 500 µL MLA pipet. Depress the pipet plunger before entering the specimen. Aspirate 500 µL (0.5 mL) of EDTA from the collection tube. Dispense the plasma into one of the amber-colored vials containing Vitamin C preservative. Using the same tip, withdraw another 500 µL (0.5 mL) amount from the same collection tube and dispense it into the second amber vial. Replace the caps and mix the specimens well. Apply seal and secure tightly with crimper provided. Place the amber vials into the rack at room temperature.
4. Replace the stopper on the lavender top blood collection tube #5 and discard in a biohazard waste bag.

11.4.4 STAGE THREE

Stage three begins approximately 30 minutes after venipuncture.

As soon as possible after the 30 minutes timer goes off, and not longer than 45 minutes after blood collection, spin tube #1 and #2 at maximum centrifugal force (not to exceed 3,000 x *g)* for 15 minutes at room temperature.

11.4.5 STAGE THREE BLOOD PROCESSING

1. Remove the red and gray top tubes from the centrifuge and place in the test tube rack.
2. Remove the stoppers from tube #1 and #2. Using a plastic transfer pipette, aliquot all of the serum equally into the ten microsample tubes.
3. Fasten red screw caps on each of these vials.
4. Replace the stoppers on the red and gray-stoppered blood collection tubes and discard in a biohazard waste bag.
5. Place the rack containing the aliquot tubes into the -70^{o}C (or -20^{o}C) freezer.

11.5 BLOOD COLLECTION AND PROCESSING (THREE MONTHS)

Collection and processing of the two blood samples is divided into 2 stages.

3 month collection supplies:

1. 4.5 mL blue-stoppered tube
2. 5 mL lavender-stoppered tube

3 month storage supplies:

2 - 2 mL polypropylene microvials
1 - Blue screw cap for microvials
1 - Purple screw cap for microvial

11.5.1 STAGE ONE: IMMEDIATE PROCESSING

At the conclusion of venipuncture, keep both tubes at room temperature.

Place tubes #1 and #2 into the centrifuge trunions. Balance the centrifuge then spin these tubes at maximum centrifugal force (not to exceed 3,000 x *g*) for 15 minutes at room temperature.

Wait for centrifuge to come to a complete stop. Remove the tubes from the centrifuge as soon as possible. Proceed to stage 2 processing.

11.5.2 OPERATING THE CENTRIFUGE

Refer to Centrifuge Operating Manual for specific operating and balancing instructions. The revolutions per minute (RPM) associated with a specific *g* rating will vary from centrifuge to centrifuge, depending on the radius of the centrifuge's rotor. To determine if your centrifuge's maximum speed exceeds 3,000 x *g*, consult the centrifuge's operating manual for the appropriate RPM setting for each centrifuge.

11.5.3 STAGE TWO:

Approximately 15 minutes after venipuncture.

11.5.3.1 Blue-stoppered Tube (Tube #1)

1. Remove tube from the centrifuge and put it in the test tube rack which contains sample aliquot tubes labeled with the corresponding participant number. Remove the stopper.
2. Using a plastic transfer pipette, take only about the top 2/3 of the plasma (the bottom 1/3 of the plasma contains platelets and we want platelet free plasma) and transfer the plasma into one 2-mL microsample tube.
3. Fasten the blue screw cap onto the vial and allow it to remain in the rack.
4. Restopper the sample collection tube #1 and discard it in a biohazard waste bag.

11.5.3.2 Lavender-stoppered Tube (Tube #2).

1. Remove the tube from the centrifuge. Remove the stopper.
2. Using the plastic transfer pipette, and being careful not to disturb the cell layer, remove the clear plasma supernatant. The pipette tip should not get any closer than one-half inch from the cells. Inspect for hemolysis, then transfer one 2.0 mL aliquot into a 2 mL microsample tube. After leaving one-half inch of plasma on the cells, any excess plasma may be discarded. *Do not overfill!*
3. Fasten the purple cap on the sample aliquot tube and place it in the rack.
4. Replace the stopper on the lavender top blood collection tube #2 and discard in a biohazard waste bag.

5 Place the rack into the -70^{o}C (or -20^{o}C) freezer.

11.6 BLOOD COLLECTION AND PROCESSING (18 MONTHS)

Collection and processing of the various blood samples is divided into 3 stages.

18 month collection supplies:

1. 10 mL red and gray-stoppered tube
2. 4.5 mL blue-stoppered tube
3. 5 mL lavender-stoppered tube (light-protected, ice)
4. 5 mL lavender-stoppered tube

18 month storage supplies:

11 - 2 mL polypropylene microvials
2 - 2 mL amber glass vials with septa and seal
5 - Red screw caps for microvials
1 - Blue screw caps for microvials
5 - Purple screw caps for microvials

11.6.1 STAGE ONE: IMMEDIATE PROCESSING

At the conclusion of venipuncture keep all the tubes at room temperature except tube #3 which is placed into ice water.

Tube #1 remains incubating at room temperature for thirty minutes to allow the blood to clot (blood at 4°C clots extremely slowly). Set a timer for 30 minutes as a reminder to centrifuge this tube.

Place tubes #2, #3, and #4 into the centrifuge trunions. Balance the centrifuge then spin these tubes at maximum centrifugal force (not to exceed 3,000 x *g)* for 15 minutes at room temperature.

Wait for centrifuge to come to a complete stop. Remove the tubes from the centrifuge as soon as possible. Proceed to stage 2 processing.

11.6.2 OPERATING THE CENTRIFUGE

Refer to Centrifuge Operating Manual for specific operating and balancing instructions. The revolutions per minute (RPM) associated with a specific *g* rating will vary from centrifuge to centrifuge depending on the radius of the centrifuge's rotor. To determine if your centrifuge's maximum speed exceeds 3,000 x *g*, consult the centrifuge's operating manual for the appropriate RPM setting for each centrifuge.

11.6.3 STAGE TWO:

Approximately 15 minutes after venipuncture.

11.6.3.1 Blue-stoppered Tube (Tube #2)

1. Remove tube from the centrifuge and put the tube in the test tube rack which contains one sample aliquot tube labeled with the corresponding participant number. Remove the stopper.
2. Using a plastic transfer pipette, take only about the top 2/3 of the plasma (the bottom 1/3 of the plasma contains platelets and we want platelet free plasma) and transfer the plasma into one 2-mL microsample tube.
3. Fasten the blue screw cap onto the vial and allow it to remain in the rack.
4. Restopper the sample collection tube # 2 and discard it in a biohazard waste bag.
5. Leave the rack holding the filled aliquot vial at room temperature until it is time to remove the serum from tube #1.

11.6.3.2 Lavender-stoppered Tube (Tube #4).

1. Remove the tube from the centrifuge. Remove the stopper.
2. Using the plastic transfer pipette, and being careful not to disturb the cell layer, remove the clear plasma supernatant from tubes #4. The pipette tip should not get any closer than one-half inch from the cells. Inspect for hemolysis, then transfer four 0.5 mL aliquots into 2.0-mL microsample tube and one 1.0 mL aliquot into 2.0 mL microsample tubes and one 1.0 mL aliquot into a 2.0 mL microsample tube. After leaving one-half inch of plasma on the cells, any excess plasma may be added to the tubes. *Do not overfill!*
3. Fasten the purple caps on the sample aliquot tubes and place them in the rack.
4. Replace the stoppers on the lavender top blood collection tube #4 and discard in a biohazard waste bag.
5. Leave the rack holding the aliquot vials at room temperature until tube #1 is ready. They are to remain at room temperature until frozen.

11.6.3.3 Lavender-stoppered Tube (Tube #3, light protected)

1. During centrifugation, volumetrically deliver 1.5 mL Vitamin C preservative (provided by the CBL) into each of two amber-colored Wheaten vials. To deliver 1.5 mL, place a disposable plastic tip onto the 500 µL (0.5 mL) MLA pipet. Aspirate the solution and dispense it into a

vial. Repeat this step two more times, dispensing into the same vial. Repeat this procedure with the second vial. Discard the tip. Replace the caps (septa) until ready to pipet the EDTA plasma.

2. Remove the lavender light - protected tube from the centrifuge. Remove the stopper.
3 Place a clean plastic tip onto the 500 µL (0.5 mL) MLA pipet. Depress the pipet plunger before entering the specimen. Aspirate 500 µL (0.5 mL) of EDTA from the collection tube. Dispense the plasma into one of the amber-colored vials containing Vitamin C preservative. Using the same tip, withdraw another 500 µL (0.5 mL) amount from the same collection tube and dispense it into the second amber vial. Replace the caps and mix the specimens well. Apply seal and secure tightly with crimper provided. Place the amber vials into the rack at room temperature.
4. Replace the stopper on the lavender top blood collection tube #3 and discard in a biohazard waste bag.

11.6.4 STAGE THREE

Stage three begins approximately 30 minutes after venipuncture.

As soon as possible after the 30 minutes timer goes off, and not longer than 45 minutes after blood collection, spin tube #1 at maximum centrifugal force (not to exceed 3,000 x *g*) for 15 minutes at room temperature.

11.6.5 STAGE THREE BLOOD PROCESSING

1. Remove the red and gray top tube from the centrifuge and place in the test tube rack.
2. Remove the stopper from tube #1. Using a plastic transfer pipette, aliquot all of the serum equally into the five microsample tubes.
3. Fasten red screw caps on each of these vials.
4. Replace the stopper on the red and gray-stoppered blood collection tube and discard in a biohazard waste bag.
5 Place the rack into the -70^{o}C (or -20^{o}C) freezer.

11.7 BLOOD COLLECTION AND PROCESSING (36 MONTHS)

Collection and processing of the various blood samples is divided into 3 stages.

36 month collection supplies:

1. 10 mL red and gray-stoppered tube
2. 10 mL lavender-stoppered tube
3. 5 mL lavender-stoppered tube (light-protected, ice)
4. 5 µL capillary tube in 2 mL lavender stoppered Sample Prep vial

36 month storage supplies:

16 - 2 mL polypropylene microvials
2 - 2 mL amber glass vials with septa and seal
8 - Red screw caps for microvials
8 - Purple screw caps for microvials
1 - 1mL sample prep vial for HbA1c

11.7.1 STAGE ONE: IMMEDIATE PROCESSING

At the conclusion of venipuncture, keep all the tubes at room temperature except tube #3 which is placed into ice water.

Tubes #1 remains incubating at room temperature for thirty minutes to allow the blood to clot (blood at 4°C clots extremely slowly). Set a timer for 30 minutes as a reminder to centrifuge these tubes.

Immediately after all collection tubes are filled and before tube #1 has begun to clot, remove the stopper from tube #1. With a plastic disposable pipette provided, withdraw a very small amount of blood from tube #1 and place one drop on a square of Parafilm™ provided. Take one 5 µL capillary out of the capillary dispenser and attach it in the capillary holder. Touching the capillary tube to the blood drop, fill the capillary with blood end-to-end, being careful to remove any residual blood drops on the outside of the capillary. Transfer the filled capillary into the Sample Preparation vial. Cap the vial and shake it to rinse the blood completely from the capillary. **It is extremely important that no blood remains in the capillary.** Place in rack in refrigerator. This is tube #4. Replace the stopper on tube#1 and allow to clot for thirty minutes.

Place tubes #2 and #3 into the centrifuge trunions. Balance the centrifuge then spin these tubes at maximum centrifugal force (not to exceed 3,000 x *g)* for 15 minutes at room temperature.

Wait for centrifuge to come to a complete stop. Remove the tubes from the centrifuge as soon as possible. Proceed to stage 2 processing.

11.7.2 OPERATING THE CENTRIFUGE

Refer to Centrifuge Operating Manual for specific operating and balancing instructions. The revolutions per minute (RPM) associated with a specific *g* rating will vary from centrifuge to centrifuge depending on the radius of the centrifuge's rotor. To determine if your centrifuge's maximum speed exceeds 3,000 x *g*, consult the centrifuge's operating manual for the appropriate RPM setting for each centrifuge.

11.7.3 STAGE TWO:

Approximately 15 minutes after venipuncture.

11.7.3.1 Lavender-stoppered Tube (Tube #2).

1. Remove the tube from the centrifuge. Remove the stopper.
2. Using the plastic transfer pipette, and being careful not to disturb the cell layer, remove the clear plasma supernatant from tube #2. The pipette tip should not get any closer than one-half inch from the cells. Inspect for hemolysis, then transfer six 0.5 mL aliquots into 2 mL microsample tube, one 1.0 mL aliquot into a 2 mL microsample tube and one 2.0 mL aliquot into a 2 mL microsample tube. If, after leaving one-half inch of plasma on the cells, any excess plasma may be added to the tubes. *Do not overfill!*
3. Fasten the purple caps on the sample aliquot tubes and place them in the rack.
4. Replace the stopper on the lavender top blood collection tube #2 and discard in a biohazard waste bag.
5. Leave the rack holding the aliquot vials at room temperature until tube #1 is ready. Remove one 0.5 mL aliquot tube and place it into the refrigerated rack with tube #4. All other aliquot tubes are to remain at room temperature until frozen.

11.7.3.2 Lavender-stoppered Tube (#3 light protected)

1. During centrifugation, volumetrically deliver 1.5 mL Vitamin C preservative (provided by the CBL) into each of two amber-colored Wheaten vials. To deliver 1.5 mL, place a disposable plastic tip onto the 500 µL (0.5 mL) MLA pipet. Aspirate the solution and dispense it into a vial. Repeat this step two more times, dispensing into the same vial. Repeat this procedure

with the second vial. Discard the tip. Replace the caps (septa) until ready to pipet the EDTA plasma.

2. Remove the lavender light-protected tube from the centrifuge. Remove the stopper.
3 Place a clean plastic tip onto the 500 µL MLA pipet. Depress the pipet plunger before entering the specimen. Aspirate 500 µL (0.5 mL) of EDTA from the collection tube. Dispense the plasma into one of the amber-colored vials containing Vitamin C preservative. Using the same tip, withdraw another 500 µL (0.5 mL) amount from the same collection tube and dispense it into the second amber vial. Replace the caps and mix the specimens well. Apply seal and secure tightly with crimper provided. Place the amber vials into the rack at room temperature.
4. Replace the stopper on the lavender top blood collection tube #3 and discard in a biohazard waste bag.

11.7.4 STAGE THREE

Stage three begins approximately 30 minutes after venipuncture.

As soon as possible after the 30 minutes timer goes off, and not longer than 45 minutes after blood collection, spin tube #1 at maximum centrifugal force (not to exceed 3,000 x *g)* for 15 minutes at room temperature. Record the time when centrifugation begins on the Venipuncture form.

11.7.5 STAGE THREE BLOOD PROCESSING

1. Remove the red and gray top tube from the centrifuge and place in the test tube rack.
2. Remove the stopper from tube #1. Using a plastic transfer pipette, aliquot all of the serum equally into the eight microsample tubes.
3. Fasten red screw caps on each of these vials.
4. Replace the stopper on the red and gray-stoppered blood collection tube and discard in a biohazard waste bag.
5. Place the rack containing the aliquot tubes into the -70^{o}C (or -20^{o}C) freezer.

11.8 STORAGE AND SHIPPING

11.8.1 PACKAGING

Each participant's blood samples are packaged in freezer storage bags according to their specimen type.

11.8.1.1 Frozen Samples for Central Laboratory

For each participant, place all the frozen serum and plasma vials of a given cap color into a 4" x 6" storage bag. Check again to make sure all tubes are labelled. Press the air out of each bag and seal. Place all sealed 4" x 6" bags into the 12" x 12" labeled bag. Expel the air from the bag and seal it. Place this bag in the Central Laboratory box in the -70^{o}C (or -20^{o}C) freezer and do not remove it until the time of shipment.

11.8.1.2 Refrigerated Samples for Central Laboratory

Place the two refrigerated purple capped tubes into their own 3" x 5" storage bag. Use individual bags for each patient. Expel the air from the bag and seal. Place all sealed 3" x 5 " bags into a 12" x 12" bag. Place this bag in the refrigerator and do not remove until time of shipment.

11.8.1.3 Laboratory Forms

Make two copies of the completed Venipuncture Form. Send the original document to the Coordinating Center. Keep one copy at the field center, and send one copy to the Central Laboratory with the weekly specimen shipment.

Make two copies of the completed Shipment Inventory Sheet. Send the original document to the Coordinating Center. Keep one copy at the field center, and send one copy to the Central Laboratory with the weekly specimen shipment.

11.8.2 SHIPPING

The samples remain refrigerated at 4°C or frozen at -70°C (or -20°C) until they are shipped.

All specimens collected and refrigerated within the week are sent to the CBL on the following Monday via overnight Federal Express service.

All frozen sera and plasma collected and stored within the last two weeks are shipped to the Central Laboratory by overnight Federal Express service.

11.8.2.1 Packaging Instructions (refrigerated specimens)

The bag of refrigerated plasma and hemolysate are packed and shipped in cardboard covered Styrofoam boxes. Packaging instructions are as follows:

1. Place a refrigerated cool pack in the bottom of the mailer.
2. Place the 12" x 12" bag containing specimens into the Styrofoam box on top of the cool pack.
3. Place a second refrigerated cool pack on top of the specimen bag.
4. Place packing material on top of the cool pack to fill the box.
5. Place the paper shipping forms on top of the packing material. Place the lid on the styrofoam box.
6. Close and seal the outer box tightly with strapping tape. Affix biohazard label to the outside of box.
7. Address the box and contact Federal Express (1-800-GO-FEDEX) for pickup.

11.8.2.2 Packaging Instructions (frozen specimens)

The bags of frozen serum and plasma samples are packed and shipped in Styrofoam boxes. Packaging instructions are as follows:

1. Place a layer of dry ice on the bottom of the Styrofoam box.
2. Put half of the bags of sample tubes into the Styrofoam box on top of the dry ice.
3. Layer more dry ice on top of and around the sample bags.
4. Put the remaining sample bags into the Styrofoam box on top of the dry ice.
5. Layer more dry ice on top of and around the sample bags. The amount of dry ice in the shipping should total at least 5 pounds.
6. Place packing material on top of the dry ice to fill the box.
7. Place the paper shipping forms on top of the packing material. Place the lid on the Styrofoam box.
8. Close and seal the outer box tightly with strapping tape. Affix biohazard label to outside of box.
9. Address the box and contact Federal Express (1-800-GO-FEDEX) for pickup.

11.8.3 Mailing Instructions

All shipping containers are sent to the Central Laboratory by day or overnight courier to ensure receipt within 24 hours. The empty Styrofoam containers are returned to the Clinical Centers by UPS. Shipping containers to the Central Laboratory are addressed as follows:

WAVE Central Biochemistry Laboratory/University of Minnesota
Fairview-University Medical Center
Room L275 Mayo
420 Delaware Street S.E.
Minneapolis, MN 55455
Telephone: (612) 626-3391 (office)
Telephone: (612) 626-3645 (lab)
Fax: (612) 626-3489
e-mail: bucks001@maroon.tc.umn.edu

12. FORM COMPLETION AND MAILING

12.1 TYPES OF STUDY FORMS

The SCC will provide all the forms used in the study. These forms fall into two groups:

1. Forms that will become part of the official study database. These are forms W02 through W15.
2. Forms that are used during the study but will not be collected centrally at the SCC. These are:
   - The screening log (form W01)
   - The bleeding diary
   - The patient tracking form
   - All forms used by the clinics to communicate with the central angiographic lab and the central biochemistry lab
   - All forms used by the clinics, including the informed consents

12.2 LAYOUT OF STUDY FORMS W02 THROUGH W15

These study forms follow the same layout. Areas where answers need to be entered are shaded. The light shade of gray is being used to avoid problems when forms need to be faxed. The questions on the forms fall into four groups:

1. Questions where the answer is one of two possibilities. These are coded as Yes/No questions. For these questions, circle the appropriate answer (Y or N). Small "1" and "3" digits will appear next to the Y and N on the forms. These are for the benefit of the data keyers at the SCC and should be ignored.
2. Questions where the answer is one of several possibilities. These are coded with check boxes. Check the appropriate box by placing an X through it. Do not check more than one box: in the unusual case where more than one answer applies, do not check any of the boxes. Do enter a written explanation next to the question.
3. Questions where the answer is a number or a date.
4. Questions where the answer is a description ("if yes, specify", for example).

On these, please print a brief response.

12.3 MISSING DATA

The goal of the study is to collect 100% of the data for all women. When a question cannot be answered because the data are not available or not applicable, please do not leave the question blank, instead code one of the following:

- For items that are permanently missing, enter an asterisk (*) for the answer:
  - ◊ For Yes/No questions, code the asterisk between the Y and the N.
  - ◊ For check box questions, enter the asterisk *in front of* the first box, not inside the box where the keyers might interpret it as a check mark.
  - ◊ For numeric questions or dates, or text enter the asterisk anywhere within the field.
- For items that are currently missing but are expected to become available in the future, enter a question mark (?). Question mark should be placed in the same positions within items as asterisks.

Question marks should be used when most of the questions on a form have been answered and the few outstanding questions will take a long time to research. In this case, rather than delaying the entire form, you can mark the outstanding questions as temporarily missing. The SCC will send periodic reminders about any items with a question mark.

In some cases, it may be difficult to decide whether a yes/no question should be answered "No" or marked as missing. Unless otherwise specified in the manual definition for the question, the general rule is that "No" should be reserved for cases where there is sufficient reason to answer "No".

This could be either because there is enough evidence to answer "No" or because there is no reason to suspect otherwise. Situations where the answer is uncertain, but there is insufficient evidence to answer "Yes" should be coded as missing.

12.4 COMMENTS

Unusual measurements, events or circumstances should be noted on the form by writing a brief comment. If the comment refers to a particular question on the form, it should be written next to that question, if possible. If there is not enough space next to the question, write the comment on a separate piece of paper and indicate clearly which page, section number and question number the comment refers to. If the comment applies to the entire form, please this make this clear. These comments will be used by the SCC staff both for editing the data, and for additional guidance when the data are being analyzed.

12.5 DATA ENTRY AND EDITING

The data for forms W02 through W15 will be keyed at the SCC using double data entry. The SCC updates all of its official study databases on a regular weekly basis. At that time, all data forms received and keyed during the previous 7 days are also checked for consistency. This includes identifying

- values that are out of range;
- logical inconsistencies within or across forms;
- unanswered questions (other than the ones denoted by an asterisk or a question mark);
- combinations of data values within or across forms that, while they may be correct, are unusual enough to merit further explanation.

The queries that are generated by this process are first checked by the SCC staff to ensure that they are not due to local keying errors, and to determine whether comments on the study forms resolve the queries. Any queries that cannot be resolved by the SCC staff are then sent to the study coordinator.

12.6 COMPLETING AND CORRECTING STUDY FORMS

Please complete all forms legibly. Some of the study forms, particularly the medical history and quality of life forms may be completed by the participants. The study coordinator must review these forms to ensure that they were completed properly.

Any corrections to the forms should be initialed and dated (this includes corrections to copies of forms mailed to the SCC). Please be sure to complete the header at the top of each page of multi-page forms. This will minimize problems should a page become separated from the rest of the forms.

12.7 CORRECTIONS AND CHANGES TO FORMS

Forms that were sent to the SCC may need to be updated for a variety of reasons, including:

- a transcription error which is discovered either in response to a query from the SCC, or through other means
- a field that was marked temporarily missing (?) for which the value has been obtained

When a form needs to be changed, make a copy of the page of the form on which the correction is to be made and enter and initial change in red pen. Keep a second copy for your records and send the first to the SCC.

12.8 MAILING OF THE FORMS TO THE SCC

The originals (i.e. the top NCR sheet) of forms W02 through W15 should be mailed to the SCC on a weekly basis. The mailing address is:

The WAVE Statistical Coordinating Center
The GWU Biostatistics Center
6110 Executive Boulevard, Suite 750
Rockville, MD 20852

12.9 ORDERING STUDY FORMS

If a center needs additional copies of WAVE forms, the study coordinator should contact the SCC at (301) 881-9260, between 9:00 AM - 5:00 PM, EST, Monday-Friday.

13. FORM W01: SCREENING LOG

This form is no longer in use.

14. FORM W02: MEDICAL HISTORY FORM

This form may be filled out by the patient. If the patient fills out the form, then she should be instructed to answer all questions to the best of her knowledge, leaving blank any item she can't recall or is unsure about (in other words, she should not guess answers). The coordinator should review the information the patient entered to ensure that it is complete and that it was entered

properly. The coordinator will need to decide whether items that the patient left blank are to be considered permanently missing or whether they should be researched further.

14.1 IDENTIFYING INFORMATION

W*AVE Center*:
Enter the clinic number here.

***Patient Initials*:**
Enter the first three letters of the patient's last name, and first two letters of her first name.

***Number*:**
Enter the randomization number of the patient. This is obtained from the automated randomization system when the patient is randomized.

***Form Completed By*:**
Print the initials of the person who completed the form.

14.2 SECTION A: PATIENT INFORMATION

1. Date of birth:

Enter the date of birth of the patient. The date should be entered using leading zeros (e.g., 05/04/36 would indicate May 4, 1936).

2. Racial/Ethnic background:
Check the appropriate category. The categories and their definitions are as follows:

American Indian or Alaskan native: Persons having origins (ancestry) in any of the original peoples of North America and who maintain cultural identification through tribal affiliation or community recognition.

Black or African-American: Persons having origins (ancestry) in any of the Black racial groups of Africa.

Asian or Pacific Islander: Persons having origins (ancestry) in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands. This area includes, for example, China, India, Japan, the Philippine Islands, Korea, Somoa, etc.

Hispanic/Latino: Persons of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin (ancestry, regardless of race).

White not of Hispanic origin: Persons having origins (ancestry) in any of the original people of Europe, North Africa, or the Middle East.

Other: If the screenee does not identify exclusively with one of the above racial/ethnic categories, she may choose this category.

If the patient is of mixed background, she should choose the category with which she most closely identifies herself. If she cannot identify such a category, the category "Other" should be used.

3. Current Marital Status:
Check the box corresponding to the current marital status of the patient, by self-report.

***4. Level of Education*:**

Check the highest level of education the patient has *completed*.

5. Do you usually pay for your medical care through insurance?

Code Y if the patient normally uses some form of insurance. Code N if the patient does not normally use insurance. Canadian clinics should skip this question, leaving it blank.

5a. Medicare?

Code Y if the patient receives Medicare, even if she has other sources of insurance. Code N otherwise.

5b. Medicaid?

Code Y if the patient receives Medicaid, even if she has other sources of insurance. Code N otherwise.

5c. HMO (Health Maintenance Organization) for which I see my primary health care provider at the HMO building?

Code Y if the patient belongs to an HMO, even if she has other sources of insurance. Code N otherwise.

5d. PPO (Preferred Provider Organization) for which I must choose my health provider from a list, but those providers may work in private offices?

Code Y if the patient belongs to a PPO, even if she has other sources of insurance. Code N otherwise.

5e. Other private insurance (e.g. Blue Cross) for which I may choose any health provider although I may have to pay part of the fee if they are not on a preferred provider list?

Code Y if the patient has other private insurance, even if she has other sources of insurance. Code N otherwise.

14.3 SECTION B: CARDIOVASCULAR HISTORY

1. Have you had a cardiac arrest (your heart stopped and had to be restarted)?

Code Y if the patient had cardiac arrest. Code N otherwise. If the patient is not sure, this information may be confirmed by the patient's physician or medical record.

2. Have you had heart failure or congestive heart failure?

Code Y if the patient has a history of heart failure or congestive heart failure, code N otherwise. If the patient isn't sure, ask the patient if she has ever had fluid in the lungs or fluid in her legs, ankles, or feet as a result of her heart condition. This information may be obtained from the patient's physician or medical record.

3. Have you had atrial fibrillation (a type of irregular heartbeat)?

Code Y for history of atrial fibrillation, code N otherwise. This information may be obtained from the patient's physician or medical record.

4. Have you had any other type of cardiac arrhythmia (irregular heartbeat)?

Code Y for history of cardiac arrhythmias other than atrial fibrillation, code N otherwise. This information may be obtained from the patient's physician or medical record.

5. Has a doctor ever told you that you had a heart attack?

Code Y for history of myocardial infarction, code N otherwise. This may also be referred to as a "coronary". This information may be obtained from the patient's physician or medical record.

5a. If yes, when did the most recent attack occur?

Enter the date of the most recent heart attack with leading zeros. For example, May 1987 should be recorded as 05/87. If necessary, this information may be obtained from the patient's physician or medical record.

6. Have you ever had an aortic aneurysm?

Code Y for history of aortic aneurysm, code N otherwise. If the patient is not sure, this information may be obtained from the patient's physician or medical record.

7. Have you had a stroke?

Code Y for history of stroke, code N otherwise. This information may be obtained from the patient's physician or medical record. If the answer to this question is Y, the coordinator should check for type of stroke; either hemorrhagic or thrombolytic. Hemorrhagic stroke is an exclusion criterion. This information may be obtained from the patient's physician or medical record.

8. Have you ever had chest pain?

Code Y for history of chest pain, code N otherwise. This is a broad-based question and may refer chest pain of unknown or non-cardiac etiology.

8a. If yes, did a doctor ever say you had angina?

Code Y for positive medical history of angina, code N otherwise. If the participant is not sure of the etiology of her past chest pain then this information may be obtained from the patient's physician or medical record.

9. In the past four weeks have you had any chest discomfort?

Code Y if the patient has had chest discomfort in the last 4 week. Code N otherwise.

9a. If Yes, does this occur with exercise such as walking, climbing stairs, carrying something or sexual activity?

Code Y if the symptoms of chest discomfort during the past four weeks were sometimes associated with exercise.

9b. If Yes, does this occur with emotion, such as excitement, stress, tension, or anger?

Code Y if the symptoms of chest discomfort during the past four weeks were sometimes associated with emotions.

9c. If Yes, does this awaken you from sleep?

Code Y if the symptoms of chest discomfort ever awaken you from sleep.

9d. If Yes, did you have any chest discomfort at rest?

Code Y if the symptoms of chest discomfort during the past four weeks sometimes occurred while the patient was resting, or within half an hour of a meal.

9e. Choose one of three following descriptions of the typical level of your discomfort over the past 4 weeks:

Check one of the following which best fits the level of the patient's discomfort?

Ordinary physical activity does not cause angina, or angina only with strenuous or rapid or prolonged exertion.

Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, may cause angina.

Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs under normal conditions and at a normal pace may cause angina.

Inability to carry on physical activity without angina or chest pain.

10. Did your mother or any full-blooded sister have a heart attack at or before they were 65 years of age.

Code Y for positive family history of myocardial infarction in the patient's mother or full-blooded sisters before age 65. Code N otherwise.

11. Did your father or any full blooded brother have a heart attack at or before they were 55 years of age.

Code Y for positive family history of myocardial infarction in the patient's father or full-blooded brothers before age 55. Code N otherwise.

12. Did you ever have a coronary angioplasty (opening of the arteries of the heart with a balloon or other device)?

Code Y for history of coronary angioplasty or PTCA, stent, atherectomy, or other coronary intervention. Code N otherwise. If necessary, this information may be obtained from the patient's physician or medical record.

12a. If yes, when did the most recent one occur?

Enter the date the most recent coronary angioplasty was performed using leading zeros. For example: May 1987 should be recorded 05/87. If necessary, this information may be obtained from the patient's physician or medical record.

14.4 SECTION C: PERIPHERAL ARTERY DISEASE HISTORY

1. Did a doctor ever say you had claudication or peripheral arterial disease (poor blood flow to the legs or blocked or narrowed arteries in the legs)? Do not include varicose veins or phlebitis.

Code Y if the patient was diagnosed as having claudication or peripheral artery disease, not counting varicose vein and phlebitis. Code N otherwise.

1a. If Yes, have you ever had angiography (dye in the arteries of the legs)?

Code Y if the patient had angiography as a result of claudication or peripheral artery disease. Code N otherwise. If necessary, this information may be obtained from the patient's physician or medical record.

1b. If Yes, have you ever had angioplasty (balloon catheter or device to open blockage in your legs)?

Code Y if the patient had angioplasty as a result of claudication or peripheral artery disease. Code N otherwise. If necessary, this information may be obtained from the patient's physician or medical record.

1c. If Yes, have you ever had surgery to improve blood flow to your legs? (not including surgery for varicose veins)?

Code Y if the patient had surgery as a result of claudication or peripheral artery disease. Code N otherwise. If necessary, this information may be obtained from the patient's physician or medical record.

2. Did you ever have a carotid angioplasty (opening of the arteries in the neck with a balloon or other device)?

Code Y for history of carotid angioplasty, code N otherwise. If necessary, this information may be obtained from the patient's physician or medical record.

3. Have you had carotid endarterectomy (operation for blockage or narrowing of the arteries in the neck)?

Code Y for history of carotid endarterectomy, code N otherwise. If necessary this information may be obtained from the patient's physician or medical record.

14.5 SECTION D: GYNECOLOGIC HISTORY

1. How old were you when you had your first menstrual period?
Enter the age in completed years at which the patient had her first menstrual period.

2. How old were you when you last had <u>regular</u> menstrual bleeding?
Enter the age in completed years at which the patient last had regular menstrual bleeding.

3. How old were you when you last had <u>any</u> menstrual bleeding?
Enter the age in completed years at which the patient had any menstrual bleeding. If the patient still has some menstrual bleeding, enter her current age.

4. Have you ever been pregnant?
Code Y if the patient has ever been pregnant, even if she never carried the pregnancies to term. Code N otherwise.

4a. If you have, how many times?
Enter the number of pregnancies, including ectopic pregnancies or any that resulted in abortion, miscarriage, or stillborn.

4b. If you have, how many pregnancies resulted in live births?
Enter the number of pregnancies that resulted in live births.

5. Did you ever have an operation to remove one or both of your ovaries?
Code Y if the patient had an operation to remove all or part of one or both ovaries. Code N if the patient never had an operation to remove any part of her ovaries.

5a. If Yes, did the operation affect both ovaries?
Code Y if the operation removed part or all of both ovaries. Code N if only one ovary was removed.

5b. Year of the operation?
Enter the calendar year of the operation.

6. Have you had a hysterectomy (an operation to remove the uterus or womb)?
Code Y if the patient had a hysterectomy. Code N otherwise.

6a. Year of the hysterectomy:
Enter the calendar year of the operation.

7. Did you ever take birth control pills for at least 3 consecutive months?
Code Y if the patient took birth control pill regularly for a period of 3 consecutive months or more at any time in the past. Code N otherwise.

7a. If Yes, for how many total months and years?
Enter the total number of months and years that the patient took birth control pills on a regular basis.

14.6 SECTION E: HISTORY OF HIGH BLOOD PRESSURE

1. Has a doctor ever told you had high blood pressure (do <u>not</u> include high blood pressure that you only had during pregnancy)?

Code Y if the patient has a history of diagnosed hypertension, not including pregnancy induced hypertension, pre-eclampsia or eclampsia. Isolated high blood pressure readings should not be counted. Code N if the patient does not have a history of hypertension.

14.7 SECTION F: HISTORY OF DIABETES

1. Did a doctor ever tell you have diabetes or high blood sugar (do <u>not</u> include diabetes occurring only during pregnancy)?

Code Y if the patient was ever diagnosed as having diabetes, not including gestational diabetes. Code N if the patient never had a diagnosis of diabetes.

14.8 SECTION G: CANCER HISTORY

1. Has a doctor ever told you that you had endometrial cancer (cancer of the lining of uterus of womb)?

Code Y if the patient was ever diagnosed with endometrial cancer. Code N otherwise.

2. Has a doctor ever told you that you had melanoma?

Code Y if the patient was ever diagnosed with melanoma. Code N otherwise.

3. Has a doctor ever told you that you had another cancer (excluding skin cancers other than melanoma)?

Code Y if the patient was ever diagnosed with any cancer other than melanoma or endometrial cancer. Code N otherwise

14.9 SECTION H: ABDOMINAL PROBLEMS

1. Has a doctor ever told you had gallbladder disease or gallstones?

Code Y if the patient was ever diagnosed as having gallstones or gallbladder disease. Code N otherwise.

1a. If Yes, Do you now have gallbladder disease or gallstones?

Code Y if the patient currently has gallbladder disease or gallstones. Code N otherwise.

1b. If Yes, Did you ever have a procedure to remove gallstones?

Code Y if the patient has ever had a procedure to remove gallstones. Code N otherwise.

1c. If Yes, Did you have your gallbladder removed?

Code Y if the patient had her gallbladder removed. Code N otherwise.

2. Did a doctor ever say you had kidney or bladder stones?

Code Y if the patient was diagnosed with kidney or bladder stones. Code N otherwise.

3. Did a doctor ever say you had pancreatitis?

Code Y if the patient was ever diagnosed with pancreatitis. Code N otherwise.

14.10 SECTION I: BONE PROBLEMS

1. After age 55, did a health care provider ever say you had a broken, fractured or crushed bone?

Code Y if the patient had a diagnosed fracture, including stress fractures from the age of 55 on. Code N otherwise. If the patient is not 55 years old, leave this question blank.

1a. If Yes, was it in connection with a fall or an accident?

Code Y if the fracture was in connection with a fall or an accident. Code N if it was a stress fracture. If the patient had several fractures, and code Y if all of them were connected with a fall or accident. Code N if any of the fractures was a stress fracture.

1b. Was the fracture located in:

The following questions identify the location of the fracture:

1b1. the hip?

Code Y if the fracture(s) included the hip. Code N if the patient has not had a hip fracture.

1b2. the spine?

Code Y if the fracture(s) included the spine. Code N if the patient has not had a spine fracture.

1b3. another location?

Code Y if the fracture(s) included locations other than the hip and the spine. Code N if the patient has not had a fracture other than hip or spine fractures.

1b3a. If yes, specify:

For fracture(s) in other areas than the hip or spine, indicate briefly the location of the fracture(s).

14.11 SECTION J: HEALTH HABITS

1. ***Have you smoked at least 100 (five packs) cigarettes in your entire life?***

Code Y if the patient estimates she has smoked a total of at least 100 cigarettes in her life. Code N Otherwise.

1a. On average, during all the years you smoked, how many cigarettes did you smoke per day?

Enter the estimated typical number of cigarettes a day the patient smoked during the period or periods she smoked.

1b. Do you smoke cigarettes now?

Code Y if the patient is still a smoker. Code N otherwise.

1c. Except for the times you quit, how many years have you smoked cigarettes?

Enter the total number of years that the patient smoked.

2. During your entire life, have you had at least 12 drinks of any kind of alcoholic beverage?

Code Y if the patient had more than 12 drinks in her life. Code N otherwise.

2a. If Yes, how many do you currently drink?

Select the response that corresponds most closely with current alcohol consumption patterns. The choices are:

- *I no longer drink alcohol*
- *less than one drink of an alcoholic beverage / month*
- *1-4 drinks of an alcoholic beverages / month or 1 / week*
- *8-16 drinks of an alcoholic beverage / month or 2-4 / week*
- *more than 4 drinks of an alcoholic beverage / week*

3. How often each week (7 days) do you usually do the exercises below?

3a. Strenuous or very hard exercise: You work up a sweat and your heart beats fast. (For example, aerobics, aerobic dancing, jogging, tennis, swimming laps)

3a1. How many days per week? (write 0 for none)

Enter the number of days per week that the patient usually engages in strenuous exercise. If the patient does not exercise strenuously, enter 0.

3a2. How long do you usually exercise like this during one day?

Select the category which best represents the total duration of strenuous exercise on the day the patient exercises strenuously. The choices are:

- *<20 min*

- *20-39 min*
- *40-59 min*
- *1 hour or more*

3b. Moderate exercise: Not exhausting. For example, biking outdoors, using a stationary bike or treadmill, easy swimming, calisthenics, popular or folk dancing.

3b1. How many days per week? (write 0 for none)

Enter the number of days per week that the patient usually engages in moderate exercise. If the patient does not exercise at this level, enter 0.

3b2. How long do you usually exercise like this during one day?

Select the category which best represents the total duration of moderate exercise on the day the patient does moderate exercises. The choices are:

- *<20 min*
- *20-39min*
- *40-59min*
- *1 hour or more*

3c. Mild exercise: For example, slow dancing, walking, bowling, or golf.

3c1. How many days per week? (write 0 for none)

Enter the number of days per week that the patient usually engages in mild exercise. If the patient does not do mild exercise, enter 0.

3c2. How long do you usually exercise like this during one day?

Select the category which best represents the total duration of mild exercise on the day the patient does mild exercises. The choices are:

- *<20 min*
- *20-39min*
- *40-59min*
- *1 hour or more*

14.12 SECTION K: ESTROGEN HISTORY

1. Other than birth control pills, have you ever taken estrogen and/or progesterone pills, patches, cream or injections?

Code Y if the patient has taken either estrogen or progesterone or both at any time. Code N if the patient has never taken estrogen or progesterone.

Estrogens table

For each of the six estrogens types listed in the table,

- In column b., code Y if the patient used this type of estrogen preparation at any time in her life. Code N otherwise.
- if Yes, enter the average number of days per month the patient used this type of estrogen preparation in column c.
- If Yes, Enter the total number of months and years the patient used this type of estrogen preparation in column d.

Progestins and Combinations tables

The same instructions as for the estrogens table apply here.

14.14 COMMON ESTROGENS & PROGESTINS

Hormone Replacement Therapies

Estrogens	Conjugated estrogens	Premarin, PMB (Premarin + Meprobamate)
		Generic Conjugated equine estrogens
	Synthetic estrogen pills	Diethylstilbestrol
		Ogcn (estropipate)
		Ortho-Est (estropipate)
		Menest
		Estratab
		Estropipate
		Estinyl
		Estrocon
		Estrovix
		Evex
		Femest
		Feminone
		Femogen
		Gynetone
		Hormonin
		Mediatric
		Menagen
		Menrium
		Viromone
		Milpren
		Code unknown estrogen pills in this category
	Natural estrogen pill	Estrace tablet (estradiol)
		Micronized natural estrogen
	Estrogen patch	Climara
		Estraderm
		Unknown estrogen patch
	Estrogen vaginal cream	Estrace cream
		Ortho Dienestrol cream
		Premarin cream
		Femogen cream
		Ogen cream
		Unknown estrogen cream
	Estrogen injection or implant	Diethylstilbestrol
		Deladumone
		Delestrogen
		Depo-estradiul cypionate
		Ditate
		Estinyl
		Estradin
		Estrone
		Malval
		Unknown estrogen injection

Progestins	Synthetic progesterone pills	medroxyprogesterone Amen Aygestin Curretab Cycrin Duphaston Gynorest Megace Micronor (northindrone) Norlutate Norlutin Provera Code Unknown progesterone pill in this category
	Micronized natural progesterone	Micronized progesterone
	Progesterone injection or implant	Norplant Depo-Provera
Combinations	Conjugated equine estrogen + medroxyprogesterone (continous)	Prempro
	Conjugated equine estrogen + medrozyprogesterone (cyclic)	Premphase
	Esterified estrogens + testosterone	Estratest
	Conjugated equine estrogen + testosterone	Premarin with Methyltestosterone Unknown estrogen-containing combination

14.13 SECTION L: VITAMIN HISTORY

1. Did you ever take vitamin C or multivitamin pills that include vitamin C (at least 3 times/week) for at least 3 consecutive months?

Code Y of the patient has ever taken vitamin C, regularly for more than 3 consecutive months. Code N otherwise.

1a. If Yes, or how many total months and years?

Enter the cumulative number of months and years that the patient took vitamin C.

2. Did you ever take vitamin E or multivitamin pills that include vitamin E (at least 3 times/week) for at least 3 consecutive months?

Code Y of the patient has ever taken vitamin E regularly for more than 3 consecutive months. Code N otherwise.

2a. If Yes, or how many total months and years?

Enter the cumulative number of months and years that the patient took vitamin E.

15. FORM W03: RANDOMIZATION FORM

The randomization form is used for all prospective participants attending the visit. The form should be administered by the study coordinator. The specific instructions for this form are as follows:

15.1 SECTION A: VERIFICATION OF INCLUSION CRITERIA

If the answer to any of the questions in this section is No, the patient is not eligible to be randomized in the WAVE trial.

1. Postmenopausal

Code Y if the woman

a) has had an oopherectomy at any age, or

b) < age 55 and FSH $\geq$ 40. FSH required until the woman's 55th birthday

c) is < 55 years of age. From the woman's 55th birthday and thereafter, an FSH is not required.

Code N if the woman meets none of the criteria above.

2. ***Qualifying Angiogram Within Previous Four Months***

Code Y if the patient had a qualifying angiogram within the previous 4 months. Code N otherwise.

To be acceptable, the qualifying angiogram must be obtained while the patient is hemodynamically stable, and must demonstrate at least one vessel segment with a 15-75% stenosis. The qualifying artery may not have been intervened, (dilated, atherectomized, or stented). If the angiogram was performed within two weeks of a myocardial infarction, the qualifying segment may not be the infarct segment.

3. ***Signed Informed Consent***

Code Y if patient signed an informed consent form. Code N otherwise.

15.2 SECTION B: VERIFICATION OF EXCLUSION CRITERIA

If the answer to any of the questions in this section is Yes, the patient is not eligible for randomization into the WAVE trial.

1. Creatinine >2.0 mg/dL?

Code Y if the serum creatinine is >2.0 mg/dL. Code N if the serum creatinine is $\leq$2.0 mg/dL. The serum creatinine *must* be confirmed by laboratory values.

2. Unwilling to stop concurrent hormone replacement therapy?

Code Y if the patient is on HRT and the patient is not willing to stop. Code N if the patient is either not on HRT or if the patient is on HRT and is willing to stop.

The patient should be asked if she is taking hormones: estrogen, progesterone, or both. If the patient is not sure, check this with the patient's physician, medical record (if

available) and/ or have the patient bring in all bottles of medication that she is currently taking. If on HRT for at least 3 months when screened, a wash out for at least 3 months is recommended. If on HRT less than 3 months, no wash out is necessary, however the patient can not take HRT and be in the trial..

3. Unwilling to stop Vitamin C and/or E supplements ≥ Recommended Daily Allowance (RDA)?

Code Y if the patient gives any indication that she will take vitamin supplements other than those provided by the study. Code N otherwise.

If the patient is currently taking vitamins, she should be reminded that the study will provide a multivitamin which meets the RDA.

4. ***Planned or prior coronary artery bypass grafting?***

Code Y for history of coronary artery bypass surgery or if the patient is scheduled for coronary artery bypass surgery or states that her physician is planning to schedule her for this surgery. Code N otherwise.

This information can be obtained from the patient's physician and/or medical record, or from the patient.

5. ***NYHA class IV heart failure or known ejection fraction <25%?***

Code Y if the patient meets the NYHA criteria for class IV heart failure, at the time the form is completed or if the patient is *known* to have an ejection fraction of less than 25%. NYHA class IV heart failure is defined as the inability to carry out any physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. Code N if the patient does not meet the NYHA criteria for class IV heart failure AND the ejection fraction is either unknown or at least 25%.

NYHA class IV heart failure is defined as: patients who have symptoms of heart failure at rest. The patient may have one or more of the following symptoms at rest: dyspnea, paroxysmal nocturnal dyspnea, orthopnea, Cheyne-Stokes respiration, and extreme fatigue and weakness. The patient may also exhibit cerebral symptoms such as alterations in mental state characterized by confusion, difficulty in concentration, impairment of memory, headache, insomnia, and anxiety.

Acceptable documentation of ejection fraction includes a cardiac catheterization report, radionuclide scan report, or echocardiogram report, all of which must include a numeric ejection fraction. Code Y if the ejection fraction is known and is less than 25%.

6. MI less than 4 weeks prior to randomization?

Code Y if the patient has had an MI within 4 weeks preceding randomization. Code N otherwise.

This information can be obtained from the patient's physician and/or medical record. Patient history is acceptable and may be coded Y if the patient is sure that she has had an MI within 4 weeks preceding randomization. The term "heart attack" may be the wording of choice to be used when questioning patients regarding MI. The patient should also be asked if she was admitted to the hospital for the "heart attack." If the clinical coordinator is in doubt about whether the patient had an MI, this information *must* be obtained from the patient's physician and/or medical record.

7. Concurrent participation in another blinded clinical trial?

Code Y if the patient is currently participating in another masked clinical trial. Code N otherwise.

Participation in interventional device trial or short term post PTCA anti-thrombotic trial is permitted and should be coded N so long as follow-up angiography is not part of that trial. If the patient is participating in another type of clinical trial, but the principal investigator at the site feels the patient should be enrolled, the case should be referred to the SCC for review.

8. Symptomatic gallstones?

Code Y if the patient reports having been told she had gallstones by a physician and experiences characteristic pain or has a history of symptomatic gallstones confirmed by her physician and/or medical record. Code N otherwise.

9. History of PE or Idiopathic (DVT)?

Code Y if the patient has a positive history of pulmonary embolism (PE) or idiopathic deep venous thrombosis (DVT). Code N otherwise.

The term "blood clot(s)" can be used when asking the patient about these conditions. If the patient is unsure then the information *must* be obtained from the patient's physician and/or medical record.

10. History of hemorrhagic stroke or bleeding diathesis?

Code Y if the patient has had a stroke and it is confirmed that it was hemorrhagic, or if the patient has a positive history of bleeding disorders. Code N if the patient has no history of hemorrhagic stroke and no history of bleeding disorders.

If the patient has had a stroke, the information regarding whether it was hemorrhagic or thrombolytic *must* be obtained from the patient's physician and/or medical record. Information about bleeding disorders may be obtained from the patient or their physician and/or medical record.

11. Breast cancer or mammogram suggestive of cancer?

Code Y if the patient states that she has a history of breast cancer or if the patient has a questionable mammogram. Code N otherwise. Refer to page 6-6 for additional information.

12. Known endometrial hyperplasia or abnormal uterine bleeding?

Code Y if the patient has endometrial hyperplasia confirmed by endometrial biopsy, or has been told by her physician that she has abnormal uterine bleeding. Code N otherwise.

13. History of endometrial carcinoma without hysterectomy?

Code Y if the patient has a history of endometrial carcinoma and has not had a hysterectomy. Code N if she has had a hysterectomy or if she has no history of endometrial carcinoma.

14. Abnormal Pap smear with dysplasia of grade CIN-I or greater?

Code Y if the patient has had an abnormal Pap smear with dysplasia of grade CIN-I or greater. Code N otherwise. This information can *only* be obtained from the patient's physician and/or medical record. See page 6-5 for additional information.

15. Documented fasting triglycerides >500 mg/dL?

Code Y if most recently documented >500 mg/dL confirmed by laboratory values ≤ four months prior to randomization. Code N if fasting triglycerides ≤500 mg/dL.

16. Uncontrolled diabetes mellitus?

Code Y if the patient has diabetes which, in the opinion of the investigator, is uncontrolled. Code N otherwise.

Note that if the patient's diabetes is controlled by the time of randomization, the patient is eligible.

17. Uncontrolled hypertension?

Code Y if the patient has hypertension, which in the opinion of the investigator, is uncontrolled. Code N otherwise.

Note that if the patient's hypertension is controlled by the time of randomization, the patient is eligible.

18. Anticipated survival <3 years

Code Y if the patient's anticipated survival is less than 3 years. Code N otherwise.

19. Unlikely to adhere to protocol in the opinion of the investigator

Code Y if, in the investigators judgment, the patient is unlikely to adhere to WAVE protocol. Code N otherwise.

20. Angiogram not meeting protocol criteria?

Code Y if the patient does not have a qualifying angiogram (see inclusion criteria). Code N otherwise.

21. ***History of osteroporosis, either untreated or treated with HRT?***

Code Y if the patient has been told by a health care provider that she has osteoporosis and is either not being treated, or is being treated with HRT. Code N if the patient does not have a history of osteoporosis, of if the osteoporosis is being treated using a non-hormonal treatment.

15.3 SECTION C: PHYSICAL MEASURES

1. Blood pressure

Sitting Blood Pressure: The patient should be seated in a quiet room for five minutes. The arm muscles should be relaxed and the forearm supported. The arm should be at the heart level when the measurement is done.

Measurement: A mercury sphygmomanometer should be used and a cuff size selected according to the circumference of the arm (AC): ordinary cuff up to AC of 33 cm, large cuff for AC of 33-41cm, and thigh cuff for AC above 41cm. The cuff is then applied evenly and firmly to the exposed upper arm. If not contraindicated, the right arm should be selected and the same side used in the future. The cuff should be inflated to about 30 mm Hg above

expected systolic blood pressure. The cuff is then slowly deflated, about 2-3 mm Hg per beat, during which time the Korotkoff sounds are listened to through a stethoscope placed over the brachial artery. The pressure at which the sounds are first heard is the systolic pressure. The diastolic pressure is defined as the pressure at which the sounds disappear. Record the value on the WAVE Randomization Form (W03).

Blood pressure should be recorded to the nearest 2 mm Hg. In the absence of digit preference, readings ending in 0, 2, 4, 6, and 8 will be equally expected.

2. *Height*:

To measure height have the patient inhale deeply, again not altering position by, for example raising the heels off the floor. Stature is measured just before the patient exhales. The measurement is recorded to the nearest half inch or full centimeter. When measuring in centimeters or inches, record the measurement *rounding down* to the nearest 0.5 centimeter or the nearest 0.25 inch. For example, a measurement of 175.8 cm would be recorded as 175.5 and a measurement of 67.3 inches would be recorded as 67.25 inches.

All measurements should be performed using the same device and consistent units of measurement.

3. *Weight*:

The patient should not wear shoes or outdoor garments. Be sure that the scale is balanced so the indicator is at zero when no weight is on the scale. The scale should be level and on a firm surface. Ask the patient to stand in the center of the scale and not to touch or support herself on anything. The patient should stand with the head erect and eyes looking straight ahead. Record the results to the nearest ounce if measuring in pounds, or tenth of a kilogram if measuring weight in kilograms.

All measurements should be performed using the same device and consistent units of measurement.

4. *Waist circumference*

To measure waist circumference, the measurer faces the subject and places the tape around the subject, in a horizontal plane, at the level of the natural waist, which is the narrowest part of the torso, as seen from the anterior aspect. In some obese subjects, it may be difficult to identify a waist narrowing. In such cases, the smallest horizontal circumference should be measured in the area between the ribs and iliac crest. The measurement should be taken at the end of a normal expiration, without the tape compressing the skin. The measurer verifies that the patient is standing erect and that the tape is horizontal. Record the measurement in inches or centimeters. When measuring in centimeters or inches, record the measurement *rounding down* to the nearest 0.5 centimeter or 0.25 inch respectively. For example, a measurement of 75.8cm would be recorded as 75.5 cm and a measurement of 38.3 inches would be recorded as 38.25 inches. For measurements less than 100 cm or 100 inches, record the measurements with leading zeros.

5. *Hip circumference*

To measure hip circumference, the measurer squats at the side of the subject so that the level of maximum extension of the buttocks can be seen. The measuring tape is placed around the buttocks in a horizontal plane at this level without compressing the skin. The zero end of the tape should be below the measurement value. The tape is in contact with the skin but does not indent the soft tissues. The measurer verifies that the patient is standing erect and that the tape is horizontal. The measurement is recorded in inches or centimeters. When measuring in

centimeters or inches, record the measurement *rounding down* to the nearest 0.5 centimeter or 0.25 inch respectively. For example, a measurement of 75.75cm would be recorded as 75.5 cm and a measurement of 38.3 inches would be recorded as 38.25 inches. For measurements less than 100 cm or 100 inches, record the measurements with leading zeros.

15.4 SECTION D: RANDOMIZATION PROCEDURE CHECKLIST

1. ***Fasting study bloods drawn?***
Code Y if fasting study bloods were drawn, code N otherwise.

1a. ***If Yes, date of sample*****:**
Enter the date of the sample using the format Month/Day/Year with leading zeros. For example, if the randomization system was called on September 4, 1997, enter 09/04/97.

2. ***Study Angiogram done?***
Code Y if study angiogram done, code N otherwise.

2a. ***If Yes, date of angiogram*****:**
Enter the date of the angiogram using the format Month/Day/Year with leading zeros. For example, if the randomization system was called on September 4, 1997, enter 09/04/97.

3. ***ECG done?***
Code Y if an ECG was done, code N otherwise.

3a. ***If Yes, date of ECG*****:**
Enter the date of the ECG using the format Month/Day/Year with leading zeros. For example, if the randomization system was called on September 4, 1997, enter 09/04/97.

15.5 SECTION E: RANDOMIZATION

1. ***Did you have a hysterectomy?***
Code Y if the patient has had a hysterectomy, code N if she has an intact uterus. This information is also recorded on form W02. Randomization will be stratified by clinical center and by whether a hysterectomy has been performed. Women with an intact uterus if randomized to active hormone replacement therapy (HRT), will be given estrogen and progestin. No documentation of hysterectomy is required.

2. ***Bottle # of HRT study medication dispensed.***
Enter the bottle number of study medication dispensed. The code will either be H, dash, two digit number (for unopposed estrogen) or M, dash, two digit number (for estrogen + medroxyprogesterone).

3. ***Bottle # of vitamin C study medication dispensed.***
Enter the bottle number of study medication dispensed. The code will be of the form C, dash, two digit number. The two digit number will be of the same as for vitamin E, but will generally not be the same as for the HRT.

4. ***Bottle # of vitamin E study medication dispensed.***
Enter the bottle number of study medication dispensed. The code will be of the form E, dash, two digit number. The two digit number will be of the same as for vitamin C, but will generally not be the same as for the HRT

5. ***Open label Multivitamin dispensed***
Code Y if multivitamins (Centrum Silver) were dispensed. Code N otherwise.

6. ***Date of randomization:***

Record the date on which the call to the SCC randomization system was made. Enter the date using the format Month/Day/Year with leading zeros. For example, if the randomization system was called on September 4, 1997, enter 09/04/97.

Please be sure to enter the patients' randomization number at the top of each form.

16. FORM W04: CURRENT MEDICATIONS FORM

The questions on this form now appear on form W07. Form W04 should still be filled out for the baseline visit as long as these continue to occur. **However, for semi-annual visits, use form W07 instead.**

For the pre-randomization visit, record medications the patient is *currently* taking or has taken in the *past year*. For the three month visit, record medications the patient is taking or has taken since randomization. Every question should be answered. For the definition of the questions, please refer to Form W07.

17. FORM W05: GYNECOLOGICAL EXAM FORM

This form should be completed before randomization, and yearly after that. Additional exams may be performed as necessary, and form W05 should then be completed as soon as the results of the exam are available.

17.1 IDENTIFYING INFORMATION

W*AVE Center*:
Enter the clinic number here.

***Patient Initials*:**
Enter the first three letters of the patient's last name, and first two letters of her first name.

***Number*:**
Enter the randomization number of the patient. This is obtained from the automated randomization system at the time the patient is randomized.

***Form Completed By*:**
Enter the initials of the person who completed the form.

17.2 SECTION A: VISIT INFORMATION

***1. Visit*:**
Select the box corresponding to this visit. For the pre-randomization visit, check the "pre-randomization" box.

***2. Date of gynecologic examination*:**
Enter the date on which the examination was performed.

3. Was this exam performed at the study clinic?
Code Y if the gynecological exam was performed at the study clinic, code N otherwise.

4. Were any gynecological abnormalities referred for follow up?
Code Y if there were any gynecological abnormalities referred for follow up. Code N otherwise.

If Yes, answer questions 4a. through 4e., and complete a separate W18 for each abnormality.

4a. Breast Exam
Code Y if there was a breast exam abnormality referred for follow up. Code N otherwise.

4b. Mammogram

Code Y if there was a mammogram abnormality referred for follow up. Code N otherwise.

4c. Pelvic Exam

Code Y if there was a pelvic exam abnormality referred for follow up. Code N otherwise.

4d. Pap Smear

Code Y if there was a pap smear abnormality referred for follow up. Code N otherwise.

4e. Endometrial

Code Y if there was an endometrial abnormality referred for follow up. Code N otherwise.

17.3 SECTION B: BREAST EXAM

Annual breast examinations are required for the study.

1. Exam performed?

Indicate for each breast whether a breast exam has been performed. Code Y if a breast exam was performed. Code N otherwise.

If Yes,

1a. Nipple discharge?

Check "No" if there was no nipple discharge. If there is nipple discharge, check "Yes, probably benign" if the discharge was deemed benign, or "Yes, possibly malignant" if a malignancy is suspected.

1b. Skin involvement?

Check "No" if there is no skin involvement. If there is skin involvement, check "Yes, probably benign" if this was deemed benign, or "Yes, possibly malignant" if a malignancy is suspected.

1c. Axillary mass?

Check "No" if there was no axillary mass. If there was an axillary mass, check "Yes, probably benign" if it was deemed benign, or "Yes, possibly malignant" if a malignancy is suspected.

1d. Breast mass (or nodules)?

Check "No" if there was no breast mass. If there was a breast mass, check "Yes, probably benign" if it was deemed benign, or "Yes, possibly malignant" if a malignancy is suspected.

If Yes,

1d1. more than one mass?

Code Y if there was more than one breast mass. Code N if there was only a single breast mass.

1d2. primary mass mobile?

Code Y if the primary breast mass was mobile. Code N otherwise.

1d3. size of primary mass:

Check the box corresponding to the size of the primary mass. The choices are:

- *< 1 cm*
- *1-3 cm*
- *> 3 cm*

17.4 SECTION C: MAMMOGRAM

Annual mammograms are required for the study. Record clinical exam notes on back of form. See page 6-6 for additional information on mammograms.

1. Was a mammogram performed?

Code Y if a mammogram was performed. Code N otherwise.

1a. If Yes, Date of mammogram:

Enter the date of the mammogram with leading zeros.

1b. Results of the mammogram (check one):

Select the appropriate box for each breast separately. The choices are listed below. These categories follow the terminology mandated as of March 1999 for FDA accredited mammography centers.

- Not Done: check this for unilateral mammograms
- Incomplete: patient needs to have additional views. Complete form W18 and update once the results of the follow up mammogram are known
- Normal or Negative
- Benign: patient has calcifications or masses, etc.
- Probable benign finding: patient needs short term follow up, usually within 6 months. If a follow up is scheduled, Complete form W18 and update once the results of the follow up mammogram are known
- Suspicious finding: patient needs biopsy. If benign finding, the patient can return to routine screening schedule.
- Malignant/Highly suggestive.

17.5 SECTION D: PELVIC EXAMINATION

Annual pelvic examinations are required for the study.

1. Was pelvic exam performed?

If pelvic exam was performed code Y, otherwise code N.

1. a. Any vulvar abnormality?

Select the appropriate response from the following:

- *No*
- *Yes, probably benign*
- *Yes, possibly malignant*

1.a. 1) If Yes, specify:

If an abnormality was found during the pelvic exam, briefly describe it.

1.b. Uterus Present?

Code Y if the patient has an intact uterus. Code N otherwise.

1.b. 1) Normal uterus size?

Code Y if the uterus is normal in size. Code N otherwise.

1.b.2) Uterine abnormality?

Select the appropriate response from the following:

- *No*
- *Yes, probably benign*
- *Yes, possibly malignant*

2a). If Yes, specify:

If an abnormality was found during the pelvic exam, briefly describe it.

1c. Could adnexae be palpated?
Code Y if the examiner was able to palpate adnexae. Code N otherwise.

1c1. If yes, abnormality?
Code Y if a mass abnormality was found. Code N otherwise.

1c1a). If Yes, specify:
If a mass abnormality was found , briefly describe it.

17.6 SECTION E: PAP SMEAR

Annual Pap smears are recommended. See page 6-5 for additional information on Pap smears.

1. Was Pap smear done?
Code Y if a Pap smear was done. Code N otherwise.

1a. Was Pap smear done at the study clinic?
Code Y if the Pap smear was done at the randomizing clinic. Code N otherwise.

1b. Date sample collected:
Enter the date the sample was collected.

1c. Results of the Pap smear
Select the appropriate response from the following

- ☐* Cervix not present
- ☐* Endocervical cells not seen. If so, 1c1) abnormal Pap smear in past 3 years?
  If "endocervical cells not seen" is chosen, code Y if the patient had an abnormal Pap smear in the past 3 years. Code N otherwise.
- ☐* Pap smear normal
- ☐* Pap smear abnormal

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1d. If results abnormal,
Questions 2) through 4) should be answered only when "Pap smear abnormal" was chosen in question 1c.

2) Atypical squamous (or glandular) cells of uncertain significance?
Code Y if these types of cells were present. Code N otherwise.

3) Dysplasia?
Code Y if the Pap smear indicated dysplasia. Code N otherwise.

3)a) If Yes, severity:
Indicate the severity of the dysplasia. The possible choices are:

- *Mild, atypia*
- *Moderate*
- *Severe*

3)b) Grade SIL: Low / Medium / High
Enter the SIL grade for dysplasia.

4) Cancer?
Code Y if cancer was diagnosed. Code N otherwise.

17.7 SECTION F: ENDOMETRIAL ASPIRATION

Endometrial aspirations are to be performed for clinical indications. Record clinical exam notes on back of form.

1. Was endometrial aspiration performed?
Code Y if an endometrial aspiration was performed. Code N otherwise.

If Yes,

1a. Date sample collected:
Enter the date on which the aspiration was performed.

1b. Was aspiration performed because of bleeding?
Code Y if excessive bleeding was a factor in performing an endometrial aspiration. Code N if the endometrial aspiration was done for reasons unrelated to bleeding.

1c. Results of aspiration (check one):
Select the category representing the results of the endometrial aspiration:

- *No endometrial tissue identified*
- *Cystic (simple) hyperplasia with atypia*
- *Insufficient specimen*
- *Adenomatous (complex) hyperplasia present*
- *Normal atrophic endometrium*
- *Adenomatous (complex) hyperplasia with atypia*
- *Normal secretory endometrium*
- *Atypia present*
- *Normal proliferative endometrium*
- *Cancer present*
- *Cystic (simple) hyperplasia present*
- *Other*

1d. If results are Other, specify:
If the answer to questions 1c. is "Other", briefly describe the results.

18. FORM W06: CHANGE OF STUDY MEDICATION FORM

Use form W06 for any dose adjustments of study medications, including the discontinuation of some or all of the study medications. Very short term changes (less than 1 week) need not be reported.

18.1 IDENTIFYING INFORMATION

W*AVE Center*:
Enter the clinic number here.

***Patient Initials*:**
Enter the first three letters of the patient's last name, and first two letters of her first name.

***Number*:**
Enter the randomization number of the patient. This is obtained from the automated randomization system at the time the patient is randomized.

***Form Completed By*:**
Enter the initials of the person who completed the form.

18.2 FORM QUESTIONS

Note: the two questions about multivitamins on the previous version of this form have been removed.

A. TIMING OF THE CHANGE

1. Visit after which the change in study medications takes effect:
Check the appropriate box to indicate the visit after the change in study medications takes place.

2. Date of this change in study medication:
Enter the date on which the patient was instructed to start a new regime of medication. This can be a date which occurs in between regular visits. The form can be submitted with the subsequent visit forms.

B. *NATURE OF THE CHANGE*

1. Current study medication schedule (include all study medications, not just those you are changing)
The questions in this section document the dosage of the study medications prior to the change. For questions 1a through 1f, enter the number of pills per week the patient is currently taking or being prescribed.

a. HRT/HRT placebo
Enter the old prescribed number of pills per week of HRT or HRT placebo. Enter 0 if the patient is not currently on HRT or HRT placebo.

b. Vitamin C/Vitamin C placebo
Enter the old prescribed number of pills per week of Vitamin C or Vitamin C placebo. Enter 0 if the patient is not currently on Vitamin C or Vitamin C placebo.

c. Vitamin E/Vitamin E placebo
Enter the old prescribed number of pills per week of Vitamin E or Vitamin E placebo. Enter 0 if the patient is not currently on Vitamin E or Vitamin E placebo.

d. MPA, 10mg
Enter the old prescribed number of pills per week open label 10 mg MPA. Enter 0 if the patient is not currently on open label 10 mg MPA.

e. MPA, 2.5mg
Enter the old prescribed number of pills per week open label 2.5 mg MPA. Enter 0 if the patient is not currently on open label 2.5 mg MPA.

f. Premarin, 0.3mg
Enter the old prescribed number of pills per week open label Premarin. Enter 0 if the patient is not currently on open label Premarin 0.3 mg.

2. New study medication schedule (include all study medications, not just those you are changing)

The questions in this section refer to the new dosage for the study medications. If there has been no change in the dosage of particular medications, enter the same values for those medications as in section 1 above.

a. HRT/HRT Placebo

Enter the new prescribed number of pill per week of HRT or HRT placebo. If the patient will not be taking HRT or HRT placebo, enter 0.

b. Vitamin C/Vitamin C placebo

Enter the new prescribed number of pill per week of vitamin C or vitamin C placebo. If the patient will not be taking vitamin C or vitamin C placebo, enter 0.

c. Vitamin E/Vitamin E placebo

Enter the new prescribed number of pill per week of vitamin E or vitamin E placebo. If the patient will not be taking vitamin E or vitamin E placebo, enter 0.

d. MPA, 10mg

Enter the new prescribed number of pills per week open label 10 mg MPA. If the patient will not be taking open label 10 mg MPA, enter 0.

e. MPA, 2.5mg

Enter the new prescribed number of pills per week open label 2.5 mg MPA. If the patient will not be taking open label 2.5 mg MPA, enter 0.

f. Premarin, 0.3mg

Enter the new prescribed number of pills per week open label 0.3 mg MPA. Enter 0 if the patient will not be taking the study supplied open label 0.3 mg MPA.

3. Is this change permanent?

Code Y if the new dosage is expected to continue for the remainder of the study. Code N if this is a temporary change which is expected to be modified later.

3a. If not permanent, how long should the participant stay on this regimen?

If the new dosage is temporary, enter the number of weeks the patient is expected to remain on this dosage. When dosage is changed again, complete a new W06.

C. *REASON FOR THE CHANGE (mark all that apply)*

1. Vaginal bleeding?

Code Y if vaginal bleeding was a factor in changing the medication dosage for the patient. Code N otherwise.

2. Suspected or diagnosed cancer?

Code Y if breast cancer, endometrial hyperplasia or other another cancer was a factor in changing the medication dosage for the patient. Code N otherwise.

3. Breast tenderness?

Code Y if breast tenderness was a factor in changing the medication dosage for the patient. Code N otherwise.

4. Mood change?

Code Y if mood change was a factor in changing the medication dosage for the patient. Code N otherwise.

5. Weight gain?

Code Y if weight change was a factor in changing the medication dosage for the patient. Code N otherwise.

6. GI distress?

Code Y if gastrointestinal distress was a factor in changing the medication dosage for the patient. Code N otherwise.

7. Non-vaginal bleeding?
Code Y if non-vaginal bleeding was a factor in changing the medication dosage for the patient. Code N otherwise.

8. Severe headaches?
Code Y if severe headaches were a factor in changing the medication dosage for the patient. Code N otherwise.

9. Open Label Medication?
Code Y if the change in medication dosage was due at least in part to considerations other than the ones covered in questions 1 through 8. Code N otherwise.

10. Immobility?
Code Y if the change in medication dosage was due to immobilization of the patient. Code N otherwise.

11. Other medical conditions?
Code Y if there were other medical reasons for the change in dosage. Code N otherwise.

11.a. If yes, specify:
Briefly indicate the consideration(s) other than 1 through 10 that led to the change in medication dosage.

19. FORM W07S: ONE AND THREE MONTH FOLLOW UP

19.1 IDENTIFYING INFORMATION

W*AVE Center*:
Enter the clinic number here.

***Patient Initials*:**
Enter the first three letters of the patient's last name, and first two letters of her first name.

***Number*:**
Enter the randomization number of the patient. This is obtained from the automated randomization system at the time the patient is randomized.

***Form Completed By*:**
Enter the initials of the person who completed the form.

19.2 SECTION A: VISIT INFORMATION

1. Visit:
Select the box corresponding to this visit.

***2. Was scheduled contact conducted*?**
Code Y if the visit was conducted. Code N if the patient missed the visit.

***2a. If yes, date of visit*:**
Enter the actual date of the visit.

2b. If Yes, type of contact:

Indicate how the visit was conducted by checking:

- **Visit**

if the patient came to the clinic.

- **Phone**

if the visit was conducted via a phone call to the patient.

- **Mail**

if the visit was conducted by mail.

2c. *If the visit was not conducted, and the window has closed*:

the main reason was:

- *Patient unavailable but is still on medication (reschedule contact/visit)*
- *Patient wants to withdraw - no further contact*
- *Patient refused further participation and is off medication (continue telephone contact)*
- *Patient is lost to follow up (contact private physician or relative)*
- *Patient died (complete outcomes form-W09)*
- *Other*

If the visit was not conducted, sections B below and form W08a need not be completed.
The window for the one-month visit is exactly 1 week (or 7 days) either before or after the date of the scheduled one month visit. The window for the three month visit is exactly 2 weeks (or 14 days) either before or after the date of the scheduled three month visit.

19.3 SECTION B: FOR ONE MONTH VISIT

1. INR done?

Code Y if an INR was done. Code N otherwise. When completing a three month visit form, leave this question and the next one blank.

1a. If yes, enter the date of the sample.

Enter the date of the INR.

19.4 SECTION C: FOR THREE MONTH VISIT

1. Study blood drawn?

Code Y if the study bloods were draw. Code N otherwise. When completing a one month visit form, leave this question and the next one blank.

***1a. If Yes, date*:**

If study bloods were drawn, enter the date.

20. FORM W07: FOLLOW UP FORM

20.1 IDENTIFYING INFORMATION

W*AVE Center*:

Enter the clinic number here.

***Patient Initials*:**

Enter the first three letters of patient's last name, and first two letters of her first name.

***Number*:**
Enter the randomization number of the patient. This is obtained from the automated randomization system at the time the patient is randomized.

***Form Completed By*:**
Enter the initials of the person who completed the form.

20.2 SECTION A: VISIT INFORMATION

***1. Visit*:**
Select the box corresponding to this visit.

***2. Date of visit*:**
Enter the actual date of the visit.

***3. Type of contact*:**
Indicate how the visit was conducted by checking:

- **Visit**
  if the patient came to the clinic.
- **Phone**
  if the visit was conducted via a phone call to the patient.
- **Mail**
  if the visit was conducted by mail.

20.3 SECTION B: ADHERENCE

This should be done at every visit while participant is on study medication.

1. # HRT pills left
Enter the number of unused HRT/HRT placebo pills.

2. # Vitamin C pills left
Enter the number of unused Vitamin C/Vitamin C placebo pills.

3. # Vitamin E pills left
Enter the number of unused Vitamin E/Vitamin E placebo pills.

20.4 SECTION C: STUDY DRUG DISPENSATION

1. ***Bottle code of HRT study medication dispensed.***
Enter the bottle number of study medication dispensed.

2. ***Bottle code of vitamin C study medication dispensed.***
Enter the bottle number of study medication dispensed

3. ***Bottle code of vitamin E study medication dispensed.***
Enter the bottle number of study medication dispensed.

4. ***Open-label Multivitamin dispensed?***
Code Y if an open-label multivitamin was dispensed. Code N otherwise.

20.5 SECTION D: PHYSICAL MEASURES

This is required at 12, 24 and 36 months. For all other visits, leave this section blank.
Note: Use same units as at randomization visit.

1. Blood pressure
Refer to section C on Form W03 for the definition. The measurement should be done using the same units as at the randomization visit.

2. *Height*:
Refer to section C on Form W03 for the definition. The measurement should be done using the same units as at the randomization visit.

3. *Weight*:
Refer to section C on Form W03 for the definition. The measurement should be done using the same units as at the randomization visit.

4. *Waist circumference*
Refer to section C on Form W03 for the definition. The measurement should be done using the same units as at the randomization visit.

5. *Hip circumference*
Refer to section C on Form W03 for the definition. The measurement should be done using the same units as at the randomization visit.

20.6 SECTION E: PROCEDURES CHECKLIST

(required at 12, 24 and 36 month visits)

1. Fasting study bloods drawn? (required at 18 and 36 months)
Code Y if fasting study bloods were drawn, code N otherwise.

1a. If Yes, date of sample:
Enter the date of the sample using the format Month/Day/Year with leading zeros. For example, if the randomization system was called on September 4, 1997, enter 09/04/97.

2. ECG done? (required at 12 and 36 months)
Code Y if an ECG was done, code N otherwise.

2a. If Yes, date of ECG:
Enter the date of the ECG using the format Month/Day/Year with leading zeros. For example, if the randomization system was called on September 4, 1997, enter 09/04/97.

2b. Was atrial fibrillation found on the ECG?
Code Y if there was evidence of fibrillation on the ECG. Otherwise, code N and skip the next question.

2b1) If atrial fibrillation, have oral anticoagulants been prescribed?
Code Y if the patient is taking or has been prescribed anticoagulants. Code N otherwise. If there was no evidence of fibrillation on the ECG, leave this question blank.

20.7 SECTION F: INTERIM MEDICAL HISTORY

This section should be completed at every contact.

1. Since the last semi-annual visit, have you had:

1a. Coronary angiogram, angioplasty (including stent) or bypass surgery?

Code Y if the patient has had any of these procedures since the last contact. Code N otherwise. If yes, find out when and where and complete the outcomes form, W09. If performed as protocol angiogram >2yrs after randomization, this may serve as exit angiogram. If not, participant will still need exit angiogram.

1b. Carotid or peripheral vascular angiogram, angioplasty (including stent) or bypass surgery?

Code Y if the patient has had any of these procedures since the last contact. Code N otherwise.

If the patient was hospitalized for any of these reasons, find out where and when and complete the outcomes form (form W09).

1c. Overnight hospitalization for any reason?

Code Y if the patient has been hospitalized overnight. Code N otherwise.

1d. Bleeding (other than associated with surgery or angioplasty) that required a blood transfusion?

Code Y if the patient has experienced such bleeding since the last contact. Code N otherwise.

1e. A fracture?

Code Y if the patient has had a fracture. Code N otherwise.

2. In the past 4 weeks, have you had any chest discomfort or shortness of breath?

Code Y if the patient has experienced chest discomfort or shortness of breath in the past 4 weeks. Code N otherwise.

If Yes,

2a. Does this usually occur with exercise, such as walking, climbing stairs, carrying something or sexual activity?

Code Y if the patient has experienced chest discomfort or shortness of breath as a result of these activities. Code N otherwise.

2b. Does this occur with emotion such as excitement, stress, tension, or anger?

Code Y if the patient has experienced chest discomfort or shortness of breath as a result of these emotions.

2c. Does this awaken you from sleep?

Code Y if the chest discomfort or shortness of breath has awoken the patient. Code N otherwise.

2d. Did you have any chest discomfort at rest?

Code Y if the patient has experienced chest discomfort or shortness of breath while at rest. Code N otherwise.

2e. Choose one of the following descriptions of the typical level of your discomfort over the past 4 weeks

Check the one description which best fits the patient's discomfort.

- *Ordinary physical activity does not cause angina, such as walking or climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.*
- *Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or during the few hours after awakening. Walking more than 2 blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.*

- *Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs under normal conditions at normal pace.*
- *Inability to carry on physical activity without discomfort or anginal symptoms present at rest*

20.8 SECTION G: CURRENT MEDICATIONS

This section records which medications have been used since the last completed routine WAVE visit. Please answer all the questions below. If the answer to some questions is unknown, write an asterisk (*) in the shaded area.

1. Lipid Lowering Agents:

1a. HMG co-A reductase inhibitor?

Code Y if the patient is currently taking or has taken an HMG co-A reductase inhibitor lipid lowering agent, code N otherwise.

1b. fibric acid derivative?

Code Y if the patient is currently taking or has taken a fibric acid derivative lipid lowering agent, code N otherwise.

1c. niacin (nicotinic acid)?

Code Y if the patient is currently taking or has taken a niacin lipid lowering agent, code N otherwise.

1d. resins?

Code Y if the patient is currently taking or has taken a resin lipid lowering agent, code N otherwise.

1e. others?

Code Y if the patient is currently taking or has taken a lipid lowering agent other than an HMG co-A reductase inhibitor, fibric acid derivative, niacin, or resin. Code N otherwise.

2. Diabetes drugs:

2a. insulin?

Code Y if the patient is currently taking or has taken insulin, code N otherwise.

2b. oral agents?

Code Y if the patient is currently taking or has taken oral hypoglycemics, code N otherwise.

3. Calcium channel blockers:

3a. dihydropyridine?

Code Y if the patient is currently taking or has taken a dihydropyridine calcium channel blocker. Code N otherwise.

3b. Other calcium channel blockers?

Code Y if the patient is currently taking or has taken calcium channel blockers other than the dihydropyridines. Code N otherwise.

4. Open label medications:

4a. Estrogen?

Code Y if the patient is taking open label Hormone Replacement Therapy, not including open label estrogen provided by WAVE. Code N otherwise

4b. Vitamin C?

Code Y if the patient is taking vitamin C other than multivitamins. Code N otherwise.

4c. Vitamin E?
Code Y if the patient is taking vitamin E other than multivitamins. Code N otherwise.

5. Other current medications:
5a. Digoxin (Lanoxin)?
Code Y if the patient is currently taking or has taken digoxin (Lanoxin). Code N otherwise.

5b. Beta blockers?
Code Y if the patient is currently taking or has taken beta blockers. Code N otherwise.

5c. Nitrates, oral or topical (excluding sublingual NTG)?
Code Y if the patient is currently taking or has taken oral or topical nitrates excluding sublingual NTG. Code N otherwise.

5d. Aspirin?
Code Y if the patient is currently taking or has taken aspirin. Code N otherwise.

5e. Other antiplatelet agents?
Code Y if the patient is currently taking or has taken antiplatelet agents other than aspirin. Code N otherwise.

5f. Warfarin (Coumadin)?
Code Y if the patient is currently taking or has taken warfarin (Coumadin). Code N otherwise.

5g. Heparin or low molecular weight heparin (enoxaparin)?
Code Y if the patient is currently taking or has taken heparin or low molecular weight heparin. Code N otherwise.

5h. ACE inhibitors?
Code Y if the patient is currently taking or has taken and angiotensin converting enzyme (ACE) inhibitor. Code N otherwise.

5i. Diuretics
Code Y if the patient is currently taking or has taken diuretics, code N otherwise.

5j. Blood pressure lowering agents other than calcium channel blockers, diuretics, Beta blockers, or ACE inhibitors?
Code Y if the patient is currently taking or has taken blood pressure lowering agents other than calcium channel blockers, diuretics, beta blockers, or ACE inhibitors, code N otherwise.

5 k. Antiarrhythmics?
Code Y if the patient is currently taking or has taken antiarrhythmics, code N otherwise.

16.3 COMMONLY USED MEDICATIONS

	Generic Name	Brand Name
Lipid Lowering Agents		
HMG co-A reductase inhibitors	lovastatin	Mevacor
	fluvastatin	Lescol
	pravastatin	Pravachol
	simvastatin	Zocor
	atorvastatin	Lipitor
Fibric acid derivatives	gemfibrozil	Lopid

Niacin	niacin (nicotinic acid)	Niacor, Nicobid, Nicolar, Slo-niacin
Resins	cholestyramine	Questran, Questran-Lite, Prevalite
	cholestipol	Colestid
Oral Hypoglemic Agents	chlorpropamide	Diabinese
	glypizide	Glucotrol
	glyburide	DiaBeta, Glynase, Micronase
	metformin	Glucophage
Calcium Channel Blockers		
Dihydropyridines	nifedipine	Procardia, Adalat
	nicardipine	Cardene
	isradipine	DynaCirc
	amlodipine	Lotrel, Norvasc
	nisoldipine	Sular
	felodipine	Plendil
	nimodipine	Nimotop
Other Calcium Channel Blockers	verapamil	Calan, Isoptin, Verelan
	bepridil	Vascor
	diltiazem	Cardizem, Dilacor, Tiazac
Digoxin	digoxin	Lanoxin
Beta Blockers	acebutolol	Sectral
	atenolol	Tenormin, Tenoretic
	betaxolol	Kerlone
	bisoprolol	Zebeta, Ziac
	carteolol	Cartrol
	labetolol	Normodyne, Trandate
	metoprolol	Lopressor, Toprol
	nadolol	Corgard, Corzide
	penbutolol	Levatol
	pindolol	Visken
	propranolol	Inderal, Inderide
	sotalol	Betapace
	timolol	Blocadren, Timolide
Nitrates	isosorbide dinitrate	Isordil, Dilatrate, Sorbitrate
	nitroglycerin	Deponit NTG, Nitro-Bid, Nitrodisc, Nitro-Dur, Transderm-Nitro
	isosorbide mononitrate	Monoket, Ismo, Imdur

Antiplatelet Agents	dipyridamole	Persantine
	ticlopidine	Ticlid
ACE Inhibitors (include ACE receptor blockers)	benezepril	Lotensin, Lotrel
	captopril	Capoten, Capozide
	enalapril	Vasotec, Vaseretic
	fosinopril	Monopril
	lisinopril	Prinivil, Prinizide, Zestril, Zestoretic
	moexipril	Univasc
	quinapril	Accupril
	ramipril	Altace
	trandolapril	Mavik
	losartan	Hyzaar, Cozaar
Diuretics	acetazolamide	Diamox
	benzthiazide	Exna
	bumetanide	Bumex
	chlorthalidone	Combipres, Hygroton, Thaliton
	ethacrynic acid	Edacrin
	furosemide	Lasix
	hydrochlorothiazide	Aldoclor, Aldoril, Apresazide, Capozide, Diuril, Dyazide, Esidrix, Aldactazide, Hydrodiuril, Maxzide, Minizide, Moduride, Oretic, Prinizide, Vaseretic, Zestoretic, Ziac
	hydroflumethazide	Diucardin
	indapamide	Lozol
	metolazone	Mykrox, Zaroxolyn
	methyclothiazide	Enduron
	quinethazone	Hydromox
	torsemide	Demadex
Other blood pressure lowering agents	doxazocin	Cardura
	terazocin	Hytrin
	prazocin	Minipress, Minizide
	methyldopa	Aldomet, Aldoclor, Aldoril
	clonidine	Catapres, Combipres
	hydralazine	Apresoline, Apresazide
Antiarrhythmics	moricizine	Ethmozine
	mexilitine	Mexitil
	disopyramide	Norpace
	procainamide	Procan SR

quinidine	Quinaglute, Quinidex
propaphenone	Rhythmol
flecanide	Tambocor
tocainide	Tonocard
amiodarone	Cordarone

21. FORM W07m: MISSED FOLLOW UP VISIT FORM

Complete this form whenever the W05, W07/W07s, or W08 will not be completed for a visit.

21.1 IDENTIFYING INFORMATION

W*AVE Center*:
Enter the clinic number here.

***Patient Initials*:**
Enter the first three letters of the patient's last name, and first two letters of her first name.

***Number*:**
Enter the randomization number of the patient. This is obtained from the automated randomization system at the time the patient is randomized.

***Form Completed By*:**
Enter the initials of the person who completed the form.

21.2 SECTION A: VISIT INFORMATION

1. Missed Visit:
Select the box corresponding to the visit that was missed.

2. Will any of the following forms be completed? (answer a. through c.)
Circle Y or N to questions a. through c. to indicate which forms will/will not be completed.

3. Was the visit missed because of an outcome (for example, a hospitalization)?
Code Y if the visit was missed because of an outcome. If yes, then complete form W09. Code N otherwise.

4. Will the patient receive or be sent the WAVE study medication for this visit?
Code Y if the patient will receive or be sent WAVE study medication. Code N otherwise. If no, you may need to complete form W06, the change of medications form.

5. Is the patient expected to come to future visits?
Code Y if the patient is going to complete the next WAVE visit. Code N otherwise.

6. If information is available regarding the reason why the visit was missed, please specify.
Enter comments into shaded box.

22. FORM W08: GYNECOLOGICAL FOLLOW UP

This form accompanies the W07s and the W07 form and contains the gynecological information collected at the one month, three month, and semi-annual visits. This form should be completed by the gynecological contact at the clinic in order to avoid unmasking WAVE staff. If the gynecological component of the visit is not conducted, form W07m should be completed.

22.1 IDENTIFYING INFORMATION

W*AVE Center*:
Enter the clinic number here.

***Patient Initials*:**
Enter the first three letters of the patient's last name, and first two letters of her first name.

***Number*:**
Enter the randomization number of the patient. This is obtained from the automated randomization system at the time the patient is randomized.

***Form Completed By*:**
Enter the initials of the person who completed the form.

22.2 SECTION A: VISIT INFORMATION

1. Visit:
Select the box corresponding to this visit.

***2. Date of contact*:**
Enter the date of the gynecological visit. This may be different from the visit date on form W07 or W07s.

22.3 SECTION B: SAFETY INTERVIEW

(complete at every visit while participant is on study medication)

Since the last routine WAVE contact:

1. Have you had any bleeding from your vagina since the last routine WAVE visit?
Code Y if the patient had vaginal bleeding since the last visit. Code N otherwise. Bleeding after 6 months should be followed up and reported on form W18.

1a. If yes, have you had a hysterectomy?
Code Y if the patient had a hysterectomy since the last routine WAVE visit. Code N otherwise.

2. Have you noticed any changes in your breasts (new lumps, nipple discharge, or skin changes) since the last routine WAVE visit?
Code Y if the patient has noticed any changes in her breasts since the last routine WAVE visit. Code N otherwise.

3. Since the last routine WAVE visit, have you been told that you had:

3a. breast cancer?
Code Y if the patient has been diagnosed as having breast cancer since the last routine WAVE visit. Code N otherwise. If yes, find out when and where, obtain records and complete outcomes form W09.

3b. endometrial cancer?
Code Y if the patient has been diagnosed as having endometrial cancer since the last routine WAVE visit. Code N otherwise. If yes, find out when and where, obtain records and complete outcomes form W09.

3c. endometrial hyperplasia?
Code Y if the patient has been diagnosed as having endometrial hyperplasia since the last routine WAVE visit. Code N otherwise. If yes, find out when and where, obtain records and complete outcomes form W09.

3d. blood clots in your legs or lungs?
Code Y if the patient has been diagnosed as having blood clots in the legs or lungs since the last routine WAVE visit. Code N otherwise. If yes, find out when and where, obtain records and complete outcomes form W09.

3e. gallbladder disease causing abdominal pain or indigestion?
Code Y if the patient has been diagnosed as having gallbladder disease (causing abdominal pain or indigestion) since the last routine WAVE visit. Code N otherwise. If yes, find out when and where, obtain records and complete outcomes form W09.

22.4 SECTION C: ACTIONS

(complete for every visit)

1. As a result of this gynecologic evaluation, were any actions taken beyond reassuring the patient?
Code Y if actions beyond reassuring the patient were taken. Code N otherwise.

If yes, answer questions a. through e. below. If No, leave questions a. through e. blank. If follow up was recommended complete form W18.

If Yes,

1a. Were medications changed or stopped? (if so complete form W06)
Code Y if the patients' medication was changed or stopped. Code N otherwise. If any of the study medicines are being stopped permanently, complete form W06.

1b. Was the participant asked to return to the clinic for evaluation?
Code Y if the patient was asked to return for further evaluation. Code N otherwise.

1c. Was the consulting gynecologist notified?
Code Y if the consulting gynecologist was notified. Code N otherwise.

1d. Was the participant referred to a primary care physician?
Code Y if the patient was referred to a primary care physician. Code N otherwise.

1e. Were there other actions?
Code Y if other actions were taken. Code N otherwise.

1e1). If yes, specify:
Detail the actions taken.

23 FORM W09: OUTCOMES FORM

This form should be completed whenever a patient has died, been hospitalized, or has had an outpatient procedure. If several events occur on the same day, report them on the same form. If the patient was admitted, include the discharge summary and face sheet with ICD codes.

23.1 IDENTIFYING INFORMATION

W*AVE Center*:
Enter the clinic number here.

***Patient Initials*:**
Enter the first three letters of the patient's last name, and first two letters of her first name.

***Rand Number*:**
Enter the randomization number of the patient. This is obtained from the automated randomization system at the time the patient is randomized.

***Form Completed By*:**
Enter the initials of the person who completed the form.

23.2 SECTION A: HOSPITALIZATION INFORMATION

1. Status:
Check one of the following categories:

- **admitted:** If the events described on this W09 occurred during the patient's hospitalization.
- **outpatient/ER:** If the events described on this W09 occurred while the patient was in the emergency room or while she was being treated on an outpatient basis, and she was **not** admitted to the hospital as an inpatient.
- **Not hospitalized:** If the events on this W09 occurred while the patient was outside a hospital.

1a. If admitted, was it for a cardiovascular event?
If the patient was admitted, code Y for a cardiovascular event. Code N otherwise.
If the patient was not admitted, leave this question blank.

2. Date of admission, Outpatient Procedure or Event:
Enter the date of the event or hospital admission. If the patient was in the ER and then admitted, use the date of the emergency room admission as the date of the hospitalization.

3. Date of Discharge (if hospitalized):

Enter the date of discharge if the patient was hospitalized. If the events on this W09 did not occur during an admission, leave blank.

23.3 SECTION B : OUTCOMES

Answer questions 1 through 20. All Y or N answers are to be answered for the event, not for the required documentation.

1. Death?

Code Y if the patient died. Code N otherwise.
Attach the death certificate to the form.

a. Autopsy?

Code Y if an autopsy was performed. Code N otherwise. If the patient did not die, leave blank.
Attach the autopsy report to the form.

2. Breast Cancer?

Code Y if the patient has been diagnosed with breast cancer. Code N otherwise.
Attach the pathology report to the form.

3. Endometrial cancer?

Code Y if the patient has been diagnosed with endometrial cancer. Code N otherwise.
Attach the pathology report to the form.

4. Endometrial hyperplasia?

Code Y if the patient has been diagnosed with endometrial hyperplasia. Code N otherwise.
Attach the pathology report to the form.

5. Pulmonary embolism?

Code Y if the patient has been diagnosed with a pulmonary embolism. Code N otherwise.
Attach the diagnostic test report to the form.

6. Deep Venous Thrombosis?

Code Y if the patient has been diagnosed with deep venous thrombosis. Code N otherwise.
Attach the diagnostic test report to the form.

7. Bleeding requiring transfusion?

Code Y if the patient has required a blood transfusion. Code N otherwise. Attach the narrative summary for a major bleed without death to the form.

8. Symptomatic gall bladder disease?

Code Y if the patient has been diagnosed with symptomatic gall bladder disease. Code N otherwise. Attach the diagnostic test report to the form.

9. Number of Acute Myocardial Infarctions:

Enter the number of MI's the patient had during this hospitalization. Attach the cardiac enzyme report, and the first and last ECG for each MI. Enter 0 if the patient did not have an MI.

10. Stroke?

Code Y if the patient had a stroke. Code N otherwise.
Attach the face sheet with ICD codes to the form.

11. Heart Failure?

Code Y if the patient experienced heart failure. Code N otherwise.
Attach the face sheet with ICD codes to the form.

12. Number of coronary angiograms?

Enter the number of coronary angiograms the patient had during this hospitalization. Enter 0 if the patient had no angiograms. Attach the angiography report(s) to the form. Please note that all films must be sent to the CAL as soon as possible.

13. Coronary angioplasty or stent?

Code Y if the patient underwent a coronary angioplasty or stent. Code N otherwise.
Attach the angioplasty or operative report to the form.

14. Coronary artery bypass grafting?

Code Y if the patient underwent a coronary artery bypass graft. Code N otherwise.
Attach the operative report to the form.

15. Carotid angiography?

Code Y if the patient has had a carotid angiography. Code N otherwise.
Attach the angiography report to the form.

16. Carotid angioplasty or stent?

Code Y if the patient underwent a carotid angioplasty or stent. Code N otherwise.
Attach the angioplasty or operative report to the form.

17. Carotid endarterectomy?

Code Y if the patient underwent a carotid endarterectomy. Code N otherwise.
Attach the operative report to the form.

18. Peripheral vascular angiography?

Code Y if the patient has had a peripheral vascular angiography. Code N otherwise.
Attach the angiography report to the form.

19. Peripheral vascular angioplasty or stent?

Code Y if the patient underwent a peripheral vascular angioplasty or stent. Code N otherwise.
Attach the angioplasty or operative report to the form.

20. Peripheral vascular bypass grafting?

Code Y if the patient underwent a peripheral vascular bypass graft. Code N otherwise.
Attach the operative report to the form.

24 FORMS W10 THROUGH W14 (QUALITY OF LIFE)

The purpose of the quality of life assessment is to quantitatively assess the qualitative consequences of a patient participating in the WAVE clinical trial. At the same time, it will characterize the impact of various intervening events (e.g., repeat angiography) on the patient's assessment of their quality of life. This second objective will be assessed by use of the "response shift" methodology. Several questionnaires are being used and it is going to be important to administer these questionnaires in as consistent and practical manner as possible, across and within sites. Administering a questionnaire is like repeating an experiment. Unless it is implemented in a reasonably consistent manner, one cannot expect consistent results.

The basic issues to remember in administering questionnaires is that the patient must be given the opportunity to fill out the questionnaires in an environment and under time constraints which are realistic. Thus, if the patients are to do it in a clinical environment, it is going to be important for the patients to have sufficient amount of time to complete the questionnaire. In addition, the administrator should review each questionnaire to make sure that all sections are completed and to encourage the patient to complete the sections which are not. It would be useful to know why a patient is refusing to answer any particular item or set of items. This information can be recorded on the questionnaire itself or noted and shared with the local principal investigator who will communicate it to the WAVE staff.

The quality of life questionnaires will be administered four times during the course of the study. Patients will receive the complete battery five assessment instruments at baseline (immediately after randomization), then at 18 and 30 months. Two questionnaires, the Seattle Angina Questionnaire and the Duke Activity Status Index, will be administered alone after 3 months.

24.1 PROCEDURE:

Each patient will be presented with a packet of appropriate forms at the time that they receive the Quality of Life assessment. The test administrator should have available either pencils or ball point pens that the patient can use if they do not have any of their own. Thus, adequate space and time should also be provided the patient. If it is possible for the patient to respond to the questionnaires in a quiet environment, then that would be preferred. The administrator of the package should present the package to the patient and go through the package informing them of the five sub-tests and review the instructions which are contained for each test.

After the patient has completed the questionnaire, the administrator should inspect the questionnaire booklet and determine if there are any unanswered questions. It is appropriate and would be quite helpful if the administrator would try to determine the reason for non-responses. This information can be recorded as comments on the form. Occasionally, patients will not have sufficient time to complete the questionnaire which we estimate will take at least half-hour, but less than 3/4 hour. We expect that a patient with cognitive limitations may take more time. If time is an issue, you may consider mailing the package to the patient prior to the visit and ask the patient to complete the forms and bring them to the visit. You may also consider sending the questionnaire package home with the patient to complete and return to you by mail. However, by doing that you create a number of problems for yourself including insuring that the patient will be compliant and return the questionnaire. Thus, if you opt for sending the questionnaire home with the patient, then it is going to be important that you prepare a follow-up phone call optimally optimally within several days of the patient's visit to remind the patient and determine whether

they have completed the questionnaire and sent it in. It would also be very helpful to include a self-addressed envelope with the questionnaire so that the patient doesn't have the burden of cost or of having to return the questionnaire to a post office. By sending the questionnaire home, you make more difficult for yourself the task of reviewing the responses to the questionnaire and inquiring about any missing items. However, it would be quite helpful for you to call the patient and make an attempt to determine the patient's answer to items to which they have not responded. You should record the date that any packages are received back from the patient since this will give us an estimate of how much delay there is between the original administration and the return of the questionnaires to you. This is particularly critical at baseline where patient's long lapses in filling out the questionnaire, they may end up being in a position of out several questionnaires within a relatively short time frame, meaning at baseline and at 3 months post-entry into the trial.

24.2 RESPONSE SHIFT ASSESSMENT

At the 30 month visit, you are going to be asked to administer one assessment instrument, the MOS-36 twice. This second administration is to provide an estimate of whether a response shift has occurred. By response shift we mean whether the patient's criteria that they are using to respond to their current quality of life has been modified as a result of the experiences they have had. Thus, after administering the original booklet with all of the tests, you are to administer the MOS-36 alone asking the patient to think about what it was like when they originally started the study and to answer the questionnaire in those terms. Ultimately, we will compare their projective responses to actual response at baseline to determine if in fact the criteria they are using for estimating where they were has changed. This should take the patient an additional ten minutes and should only be introduced after the patient has completed the original battery. This approach insures that the initial battery will be completed independent of this second task.

24.3 SPECIFIC INSTRUCTIONS AND DEFINITIONS

General instructions for completing the forms, when appropriate, have been written directly on the forms. The exception is for the second administration of the MOS-36: the same instructions as were given for the original MOS-36 should be used, but in addition, the patient should be told the following:

> *Please answer this questionnaire again, but now attempt to answer it in terms of what you remember to be true for you at the time you started this study 30 months ago.*

25 FORM W15: PROTOCOL DEVIATION FORM

25.1 IDENTIFYING INFORMATION

W*AVE Center*:
Enter the clinic number here.

***Patient Initials*:**
Enter the first three letters of the patient's last name, and first two letters of her first name.

***Number*:**
Enter the randomization number of the patient. This is obtained from the automated randomization system at the time the patient is randomized.

***Form Completed By*:**

Enter the initials of the person who completed the form.

25.2 FORM QUESTIONS

***1. Type(s) of protocol deviation*:**

1a. Unblinding:
Code Y if the patient's treatment allocation (active drugs versus placebo) was felt to have been disclosed. This could happen for example, if the patient discusses gynecological symptoms attributable to estrogen with anyone other than the gynecological contact. Code N otherwise.

1b. Open label estrogen
Code Y if the patient has received open label estrogen. Open label estrogen prescribed by WAVE staff as per protocol should not be reported here. Code N otherwise.

1c. Open label progesterone
Code Y if the patient has received open label progesterone. Open label progesterone prescribed by WAVE staff as per protocol should not be reported here. Code N otherwise.

1d. Open label vitamins
Code Y if the patient has received vitamin C or vitamin E in doses exceeding the daily recommended allowance.

1e. Other
If none of items 1a through 1d apply, code Y here. Otherwise code N.

1e1. If Other, specify:
Describe the protocol violation. If you need more space than is available on the form, use additional pages.

***2. Date of protocol deviation*:**
Enter the date on which the protocol violation occurred.

***3. Circumstances of protocol deviation: Describe why the protocol deviation occurred (for example, adverse events), who was involved and what happened*.**
Describe the circumstances that led to the protocol violation. In particular, if the deviation was mandated by medical consideration, describe them.

***4. Name of person reporting the protocol deviation*:**
Enter the name of the person filing this report. This person should also be familiar with the details of the protocol deviation and be able to answer additional questions from the SCC.

26 Form W18: GYNECOLOGIC TRACKING FORM

Use this form whenever a patient is referred for vaginal bleeding after 6 months on study medication, or for follow up for a gynecological abnormality.

26.1 IDENTIFYING INFORMATION

W*AVE Center*:
Enter the clinic number here.

***Patient Initials*:**
Enter the first three letters of the patient's last name, and first two letters of her first name.

***Rand Number*:**
Enter the randomization number of the patient. This is obtained from the automated randomization system at the time the patient is randomized.

***Form Completed By*:**
Enter the initials of the person who completed the form.

26.2 SECTION A FORM QUESTIONS

A. VISIT INFORMATION:

1. ***To which visit is this form attached?***
Check the appropriate box corresponding to this visit.

2. Date of the visit:
Enter the correct date of the visit. This should match the date on the corresponding W05 or W08 form.

3. To which abnormality is this form attached? Check one.
Check the appropriate box corresponding to the gynecologic follow up. This should match the abnormality on the corresponding W05 or W08. Use separate W18 forms for separate abnormalities.

26.3 SECTION B: GYNECOLOGICAL INFORMATION

1. ***Briefly describe the abnormality or condition that prompted the referral:***
Enter comments into the shaded box.

2. ***Briefly describe the type of follow up visit or procedure, and when it is expected to be carried out.***
Enter comments into the shaded box.

26.4 SECTION C: FOLLOW UP INFORMATION:

(Complete this section once the outcome of the follow up is known, and fax the updated form to the SCC.)

1. Date of the follow up:

Enter the date of the follow up visit.

2. Describe the outcome of the follow up:

If the follow up was not done, indicate the reason into the shaded box.

27. APPENDIX A: SAMPLE LETTERS, FORMS

Other forms may be necessary or required to be either given to the patients and/or their

physicians. Samples of these forms may be found in chapter 3. These sample forms may be used by the study sites as they are presented here in the manual of operations or each individual study site may develop its own version of these forms, instruction sheets or letters.

27.1 WAVE INSTRUCTION SHEETS

27.2.1 SAMPLE LETTER TO PRIMARY CARE PHYSICIANS

Dear Physician and Heath Care Provider,

Your patient has expressed an interest in the Women's Angiographic Vitamin & Estrogen trial (WAVE). It is important that she do this under the guidance and full knowledge of her usual health care provider. It is WAVE policy that clinics work closely with the woman's own primary care providers and gynecologists. WAVE will *not* provide primary health care to participants.

WAVE is a clinical trial funded by the National Institutes of Health which will enroll 450 postmenopausal women with coronary disease at 5 clinical sites. It will study the effect of hormone replacement therapy and vitamin E & C supplementation on angiographic coronary artery disease.

The hormone replacement therapy intervention consists of either placebo or active hormones (Premarin 0.625 mg/day for hysterectomized women without a uterus or Prempro (0.625mg of estrogen plus 2.5 mg of medroxyprogesterone)/day for women with an intact uterus). To be randomized to one of these arms, the woman must be postmenopausal, have qualifying coronary disease on protocol angiography and have no contraindications to taking hormone medications (for example, no history of hormone-related cancers such as breast and endometrial and not currently on any hormone replacement therapy). The vitamin intervention consists of either placebo or active vitamins (E 400 IU + C 500 mg, each taken twice daily). Women will be randomly assigned to one of four arms: active hormones + active vitamins, active hormones + vitamin placebo, hormone placebo + active vitamins or hormone placebo + vitamin placebo. Neither the investigators nor the participants can choose their treatment assignment or will know what they are taking.

If a woman currently on hormones is interested in participating, it is necessary for her to "wash out" of her medications for three months prior to entering. This would mean that she would taper down and then be off all hormones for these three months. Some women might experience some perimenopausal-type symptoms that you could treat symptomatically. Others might have severe persistent symptoms of hormone withdrawal. Severe symptoms would make a woman ineligible for the trial because she would not be able to tolerate being randomized to placebo. No washout is required for women currently taking vitamins E or C.

Once your patient has been enrolled in WAVE, it is important that any estrogen, progestin, vitamin C or E treatment she receives is according to the protocol. She should generally not receive any estrogen or progestin other than those she has been randomized to receive in the trial, since these will interfere with the evaluation of the trial results, and could also result in the woman receiving an excessive overall dose of hormone. This "rule" applies to all forms of estrogen, including the patch and vaginal creams. However, there may be occasions when symptoms necessitate short courses of non-trial hormone medications. Vitamin C and E use beyond that prescribed for the trial is limited to the recommended daily allowance, that is vitamin

E 30 IU/day and vitamin C 60 mg/day. We would like to work with you to resolve such symptoms symptoms in a manner consistent with the WAVE protocol.

WAVE will follow your patient for approximately 3 years. To assure participant safety and appropriate data collection, she will have yearly anthropometric evaluation, clinical breast exam, mammogram, pelvic exam and Pap smear. The costs of these exams and tests will be covered by the study. All results of these studies will be forwarded to your office upon receiving your patient's signed permission. If any problem is found during these exams or your patient should develop any problems not related to HRT, she will be referred back to your office for care. It may be possible for you to perform or arrange some of these yearly exams, including mammogram and Pap smears. At the end of the trial, your patient will have a repeat coronary angiogram for comparison with that obtained at the study entry.

The participation of your patient will have considerable impact upon the future of health care for all women. Your support and collaboration are critical to the success of WAVE and our ability to answer important questions on women's health. If you should have any questions regarding WAVE, please call me at _____.

Sincerely,
Principal Investigator

28. APPENDIX B: ICD-9 CODES

410 - ACUTE MYOCARDIAL INFARCTION

410.0 Of anterolateral wall
410.1 Of other anterior wall
  Infarction:
    anterior (wall) NOS (with contiguous portion of intraventricular septum)
    anteroapical (with contiguous portion of intraventricular septum)
    anteroseptal (with contiguous portion of intraventricular septum)
410.2 Of inferolateral wall
410.3 Of inferoposterior wall
410.4 Of other inferior wall
  Infarction:
    diaphragmatic wall NOS (with contiguous portion of intraventricular septum)
    inferior (wall) NOS (with contiguous portion of intraventricular septum)
410.5 Of other lateral wall
  Infarction:
    apical-lateral
    basal-lateral
    high lateral
    posterolateral
410.6 True posterior wall infarction
  Infarction:
    posterobasal
    strictly posterior
410.7 Subendocardial infarction
  Nontransmural infarction
410.8 Of other specified sites
  Infarction of:

atrium
papillary muscle
septum alone

410.9 Unspecified site
Acute myocardial infarction NOS
Coronary occlusion NOS

411 OTHER ACUTE AND SUBACUTE FORMS OF ISCHEMIC HEART DISEASE

411.0 Postmyocardial infarction syndrome
Dressler's syndrome

411.1 Intermediate coronary syndrome
Impending infarction
Preinfarction angina
Preinfarction syndrome
Unstable angina

411.8 Other

411.81 Coronary occlusion without myocardial infarction
Coronary (artery):
embolism without or not resulting in myocardial infarction
occlusion without or not resulting in myocardial infarction
thrombosis without or not resulting in myocardial infarction

411.89 Other
Coronary insufficiency (acute)
Subendocardial ischemia

412 OLD MYOCARDIAL INFARCTION

Healed myocardial infarction
Past myocardial infarction diagnosed on ECG [EKG] or other special investigation, but currently presenting no symptoms

413 ANGINA PECTORIS

413.0 Angina decubitus
Nocturnal angina

413.1 Prinzmetal angina
Variant angina pectoris

413.9 Other and unspecified angina pectoris
Angina:
NOS
cardiac
of effort
Anginal syndrome
Status anginosus
Stenocardia
Syncope anginosa

414 OTHER FORMS OF CHRONIC ISCHEMIC HEART DISEASE

414.0 Coronary atherosclerosis
Arteriosclerotic heart disease [ASHD]
Atherosclerotic heart disease
Coronary (artery):

arteriosclerosis
arteritis or endarteritis
atheroma
sclerosis
stricture

414.00 Of unspecified type of vessel, native or graft
414.01 Of native coronary artery
414.02 Of autologous biological bypass graft
414.03 Of nonautologous biological bypass graft
414.04 Of artery bypass graft
Internal mammary artery
414.05 Of unspecified type of bypass graft
Bypass graft NOS

414.1 Aneurysm of heart
414.10 Of heart (wall)
Aneurysm (arteriovenous):
mural
ventricular
414.11 Of coronary vessels
Aneurysm (arteriovenous) of coronary vessels
414.19 Other
Arteriovenous fistula, acquired, of heart

414.8 Other specified forms of chronic ischemic heart disease
Chronic coronary insufficiency
Ischemia, myocardial (chronic)
Any condition classifiable to 410 specified as chronic, or presenting with symptoms after 8 weeks from date of infarction

414.9 Chronic ischemic heart disease, unspecified
Ischemic heart disease NOS

415 ACUTE PULMONARY HEART DISEASE

415.0 Acute cor pulmonale

415.1 Pulmonary embolism and infarction
Pulmonary (artery) (vein):
apoplexy
embolism
infarction (hemorrhagic)
thrombosis

415.11 Iatrogenic pulmonary embolism and infarction
incompetence of unspecified valve,unspecified cause
insufficiency of unspecified valve,unspecified cause
regurgitation of unspecified valve,unspecified cause
stenosis of unspecified valve,unspecified cause
Valvulitis (chronic)

426 CONDUCTION DISORDERS

426.0 Atrioventricular block, complete
Third degree atrioventricular block

426.1 Atrioventricular block, other and unspecified

426.10 Atrioventricular block, unspecified
Atrioventricular [AV] block (incomplete) (partial)
426.11 First degree atrioventricular block
Incomplete atrioventricular block, first degree
Prolonged P-R interval NOS
426.12 Mobitz (type) II atrioventricular block
Incomplete atrioventricular block:
Mobitz (type) II
second degree, Mobitz (type) II
426.13 Other second degree atrioventricular block
Incomplete atrioventricular block:
Mobitz (type) I [Wenckebach's]
second degree:
NOS
Mobitz (type) I
with 2:1 atrioventricular response [block]
Wenckebach's phenomenon
426.2 Left bundle branch hemiblock
Block:
left anterior fascicular
left posterior fascicular
426.3 Other left bundle branch block
Left bundle branch block:
NOS
anterior fascicular with posterior fascicular
complete
main stem
426.4 Right bundle branch block
426.5 Bundle branch block, other and unspecified
426.50 Bundle branch block, unspecified
426.51 Right bundle branch block and left posterior fascicular block
426.52 Right bundle branch block and left anterior fascicular block
426.53 Other bilateral bundle branch block
Bifascicular block NOS
Bilateral bundle branch block NOS
Right bundle branch with left bundle branch block (incomplete) (main stem)
426.54 Trifascicular block
426.6 Other heart block
Intraventricular block:
NOS
diffuse
myofibrillar
Sinoatrial block
Sinoauricular block
426.7 Anomalous atrioventricular excitation
Atrioventricular conduction:
accelerated
accessory
pre-excitation

Ventricular pre-excitation
Wolff-Parkinson-White syndrome

426.8 Other specified conduction disorders

426.81 Lown-Ganong-Levine syndrome
Syndrome of short P-R interval, normal QRS complexes, and supraventricular tachycardias

426.89 Other
Dissociation:
atrioventricular [AV]
interference
isorhythmic
Nonparoxysmal AV nodal tachycardia

426.9 Conduction disorder, unspecified
Heart block NOS
Stokes-Adams syndrome

427 CARDIAC DYSRHYTHMIAS

427.0 Paroxysmal supraventricular tachycardia
Paroxysmal tachycardia:
atrial [PAT]
atrioventricular [AV]
junctional
nodal

427.1 Paroxysmal ventricular tachycardia
Ventricular tachycardia (paroxysmal)

427.2 Paroxysmal tachycardia, unspecified
Bouveret-Hoffmann syndrome
Paroxysmal tachycardia:
NOS
essential

427.3 Atrial fibrillation and flutter

427.31 Atrial fibrillation

427.32 Atrial flutter

427.4 Ventricular fibrillation and flutter

427.41 Ventricular fibrillation

427.42 Ventricular flutter

427.5 Cardiac arrest
Cardiorespiratory arrest

427.6 Premature beats

427.60 Premature beats, unspecified
Ectopic beats
Extrasystoles
Extrasystolic arrhythmia
Premature contractions or systoles NOS

427.61 Supraventricular premature beats
Atrial premature beats, contractions, or systoles

427.69 Other
Ventricular premature beats, contractions, or systoles

427.8 Other specified cardiac dysrhythmias

427.81 Sinoatrial node dysfunction

Sinus bradycardia:
persistent
severe
Syndrome:
sick sinus
tachycardia-bradycardia

427.89 Other
Rhythm disorder:
coronary sinus
ectopic
nodal
Wandering (atrial) pacemaker

427.9 Cardiac dysrhythmia, unspecified
Arrhythmia (cardiac) NOS

428 HEART FAILURE

428.0 Congestive heart failure
Congestive heart disease
Right heart failure (secondary to left heart failure)

428.1 Left heart failure
Acute edema of lung with heart disease NOS or heart failure
Acute pulmonary edema with heart disease NOS or heart failure
Cardiac asthma
Left ventricular failure

428.9 Heart failure, unspecified
Cardiac failure NOS
Heart failure NOS
Myocardial failure NOS
Weak heart

429.2 Cardiovascular disease, unspecified
Arteriosclerotic cardiovascular disease [ASCVD]
Cardiovascular arteriosclerosis
Cardiovascular:
degeneration (with mention of arteriosclerosis)
disease (with mention of arteriosclerosis)
sclerosis (with mention of arteriosclerosis)

429.3 Cardiomegaly
Cardiac:
dilatation
hypertrophy
Ventricular dilatation

429.4 Functional disturbances following cardiac surgery
Cardiac insufficiency following cardiac surgery or due to prosthesis
Heart failure following cardiac surgery or due to prosthesis
Postcardiotomy syndrome
Postvalvulotomy syndrome

433 OCCLUSION AND STENOSIS OF PRECEREBRAL ARTERIES

The following fifth-digit subclassification is for use with category 433:

0 without mention of cerebral infarction
1 with cerebral infarction

433.0 Basilar artery
433.1 Carotid artery
433.2 Vertebral artery
433.3 Multiple and bilateral
433.8 Other specified precerebral artery
433.9 Unspecified precerebral artery
Precerebral artery NOS

434 OCCLUSION OF CEREBRAL ARTERIES

The following fifth-digit subclassification is for use with category 434:
0 without mention of cerebral infarction
1 with cerebral infarction

434.0 Cerebral thrombosis
Thrombosis of cerebral arteries
434.1 Cerebral embolism
434.9 Cerebral artery occlusion, unspecified

435 TRANSIENT CEREBRAL ISCHEMIA

Includes:[i] cerebrovascular insufficiency (acute) with transient focal neurological signs and symptoms
insufficiency of basilar, carotid, and vertebral arteries
spasm of cerebral arteries

435.0 Basilar artery syndrome
435.1 Vertebral artery syndrome
435.2 Subclavian steal syndrome
435.3 Vertebrobasilar artery syndrome
435.8 Other specified transient cerebral ischemias
435.9 Unspecified transient cerebral ischemia
Impending cerebrovascular accident
Intermittent cerebral ischemia
Transient ischemic attack [TIA]

436 ACUTE, BUT ILL-DEFINED, CEREBROVASCULAR DISEASE

Apoplexy, apoplectic:
NOS
attack
cerebral
seizure
Cerebral seizure
Cerebrovascular accident [CVA] NOS
Stroke

437 OTHER AND ILL-DEFINED CEREBROVASCULAR DISEASE

437.0 Cerebral atherosclerosis
Atheroma of cerebral arteries
Cerebral arteriosclerosis

437.1 Other generalized ischemic cerebrovascular disease
Acute cerebrovascular insufficiency NOS
Cerebral ischemia (chronic)
437.3 Cerebral aneurysm, nonruptured
Internal carotid artery, intracranial portion
Internal carotid artery NOS
437.4 Cerebral arteritis
437.5 Moyamoya disease
437.6 Nonpyogenic thrombosis of intracranial venous sinus
437.7 Transient global amnesia
437.8 Other
437.9 Unspecified
Cerebrovascular disease or lesion NOS

438 LATE EFFECTS OF CEREBROVASCULAR DISEASE

Note: This category is to be used to indicate conditions in 430-437 as the cause of late effects, themselves classifiable elsewhere. The "late effects" include conditions specified as such, or as sequelae, which may occur at any time after the onset of the causal condition.

Code first[ii] sequelae:
aphasia (784.3)
dysphasia (784.5)
hemiplegia (342.0-342.9)
paralysis (344.0-344.9)

440 ATHEROSCLEROSIS
440.0 Of aorta
440.1 Of renal artery
440.2 Of native arteries of the extremities
440.20 Atherosclerosis of the extremities, unspecified
440.21 Atherosclerosis of the extremities with intermittent claudication
440.22 Atherosclerosis of the extremities with rest pain
Any condition classifiable to 440.21
440.23 Atherosclerosis of the extremities with ulceration
Any condition classifiable to 440.21-440.22
440.24 Atherosclerosis of the extremities with gangrene
Any condition classifiable to 440.21, 440.22, and 440.23 with ischemic gangrene 785.4
440.29 Other
440.3 Of bypass graft of the extremities
440.8 Of other specified arteries
440.9 Generalized and unspecified atherosclerosis
Arteriosclerotic vascular disease NOS

441 AORTIC ANEURYSM AND DISSECTION
441.0 Dissection of aorta
Dissecting aneurysm of aorta (ruptured)
441.00 Unspecified site
441.01 Thoracic
441.02 Abdominal

441.03 Thoracoabdominal
441.1 Thoracic aneurysm, ruptured
441.2 Thoracic aneurysm without mention of rupture
441.3 Abdominal aneurysm, ruptured
441.4 Abdominal aneurysm without mention of rupture
441.5 Aortic aneurysm of unspecified site, ruptured
Rupture of aorta NOS
441.6 Thoracoabdominal aneurysm, ruptured
441.7 Thoracoabdominal aneurysm, without mention of rupture
441.9 Aortic aneurysm of unspecified site without mention of rupture
Aneurysm
Dilatation of aorta
Hyaline necrosis of aorta

442 OTHER ANEURYSM
442.81 Artery of neck
Aneurysm of carotid artery (common) (external) (internal, extracranial portion)

443 OTHER PERIPHERAL VASCULAR DISEASE
443.0 Raynaud's syndrome
Raynaud's:
disease
phenomenon (secondary)
443.1 Thromboangiitis obliterans [Buerger's disease]
Presenile gangrene
443.8 Other specified peripheral vascular diseases
443.81 Peripheral angiopathy in diseases classified elsewhere
443.89 Other
Acrocyanosis
Acroparesthesia:
simple [Schultze's type]
vasomotor [Nothnagel's type]
Erythrocyanosis
Erythromelalgia
443.9 Peripheral vascular disease, unspecified
Intermittent claudication NOS
Peripheral:
angiopathy NOS
vascular disease NOS
Spasm of artery

444 ARTERIAL EMBOLISM AND THROMBOSIS
444.0 Of abdominal aorta
Aortic bifurcation syndrome
Aortoiliac obstruction
Leriche's syndrome
Saddle embolus
444.1 Of thoracic aorta
Embolism or thrombosis of aorta (thoracic)
444.2 Of arteries of the extremities

444.21 Upper extremity
444.22 Lower extremity
Arterial embolism or thrombosis:
femoral
peripheral NOS
popliteal
444.8 Of other specified artery
444.81 Iliac artery
444.89 Other
444.9 Of unspecified artery

415 ACUTE PULMONARY HEART DISEASE
415.1 Pulmonary embolism and infarction
Pulmonary (artery) (vein):
apoplexy
embolism
infarction (hemorrhagic)
thrombosis

453 OTHER VENOUS EMBOLISM AND THROMBOSIS
453.8 Of other specified veins
453.9 Of unspecified site
Embolism of vein
Thrombosis (vein)

174 MALIGNANT NEOPLASM OF FEMALE BREAST
174.0 Nipple and areola
174.1 Central portion
174.2 Upper-inner quadrant
174.3 Lower-inner quadrant
174.4 Upper-outer quadrant
174.5 Lower-outer quadrant
174.6 Axillary tail
174.8 Other specified sites of female breast
Ectopic sites
Inner breast
Lower breast
Midline of breast
Outer breast
Upper breast
Malignant neoplasm of contiguous or overlapping sites of breast whose point of origin cannot be determined
174.9 Breast (female), unspecified

621 DISORDERS OF UTERUS, NOT ELSEWHERE CLASSIFIED
621.3 Endometrial cystic hyperplasia
Hyperplasia (adenomatous) (cystic) (glandular) of endometrium
Hyperplastic endometritis

575 OTHER DISORDERS OF GALLBLADDER

575.0 Acute cholecystitis
- Abscess of gallbladder without mention of calculus
- Angiocholecystitis without mention of calculus
- Cholecystitis without mention of calculus:
  - emphysematous (acute)
  - gangrenous
  - suppurative
- Empyema of gallbladder without mention of calculus
- Gangrene of gallbladder without mention of calculus

575.1 Other cholecystitis
- Cholecystitis without mention of calculus:
  - NOS without mention of calculus
  - chronic without mention of calculus

575.10 Cholecystitis, unspecified
- Cholecystitis NOS

575.11 Chronic cholecystitis

575.12 Acute and chronic cholecystitis

575.2 Obstruction of gallbladder
- Occlusion of cystic duct or gallbladder without mention of calculus
- Stenosis of cystic duct or gallbladder without mention of calculus
- Stricture of cystic duct or gallbladder without mention of calculus

575.3 Hydrops of gallbladder
- Mucocele of gallbladder

575.4 Perforation of gallbladder
- Rupture of cystic duct or gallbladder

575.8 Other specified disorders of gallbladder
- Adhesions (of) cystic duct gallbladder
- Atrophy (of) cystic duct gallbladder
- Cyst (of) cystic duct gallbladder
- Hypertrophy (of) cystic duct gallbladder
- Nonfunctioning (of) cystic duct gallbladder
- Ulcer (of) cystic duct gallbladder
- Biliary dyskinesia

575.9 Unspecified disorder of gallbladder