Clinical MOP
Table of Contents

Summary of Edits

Changes between Version 1.0 and 1.1:

- Adds new language to allow reserving discussion of process data to colleagues within each clinical site PI's departments or institutions.

1. Trial Policies

This section records policies that have been approved by the Steering Committee.

Protocol

The Protocol is a document that presents the scientific background, design, and governing policies of the study. Changes to the Protocol may be proposed by any member of the Steering Committee. Proposed modifications must be approved by the Steering Committee, the Data and Safety Monitoring Board, and appropriate offices at the NHLBI in the order listed. Voting on changes is done at regularly scheduled meetings and conference calls of the Steering Committee or the Data and Safety Monitoring Board. A majority vote of approval is required for each committee before forwarding to the next level. Protocol changes that affect participant eligibility or management must be submitted by each clinical center to its Institutional Review Board (IRB) according to local IRB guidelines. Changes must be approved by the IRB before being instituted at any site.

Manual of Procedures

The Manual of Procedures (MOP) is a working document that translates the Protocol into working procedures. Its goal is to describe the procedures with sufficient clarity to ensure that all clinical centers use the same examination procedures, participant management, intervention schedules, definitions, and, as far as possible, the same equipment.

The Coordinating Center is responsible for minor revisions of the MOP. Substantive changes require approval of the Steering Committee. A majority vote of approval by the Steering Committee is required for adoption of a substantive modification. A mail ballot may be used as necessary. Changes to the MOP and relevant forms are made as soon as practical and, unless otherwise noted, become effective on receipt of the revised procedures at the clinical centers.

Once accepted, the policies in the Protocol and the procedures described in the MOP must be followed by each clinical center. The Coordinating Center monitors adherence to the MOP and prepares regular reports for the Steering Committee summarizing adherence to protocol and deviations from these documents.

Protocol and Procedure Exceptions

It is the policy of the PREMIER Steering Committee not to allow exceptions to the procedures laid out in the study Protocol and Manual of Procedures. Investigators wishing exceptions should instead petition the Steering Committee to amend the Protocol and/or MOP to formally allow the exception.

Nonetheless, unusual circumstances will arise where this procedure is not practical. In these instances the PI or designee can petition the principal investigator of the Coordinating Center, or his designee, to grant the exception. This decision can further be appealed to the full Steering Committee. The Coordinating Center will maintain and regularly circulate a list of allowed and disallowed exceptions, as well as a list of clarifications to the Protocol and MOP.

Institutional Review Board (IRB)

The Coordinating Center and each clinical center must obtain permission from its local IRB to conduct the study before beginning recruitment. As noted above, all changes to the Protocol must also be submitted for IRB review and approval according to local IRB guidelines. Documentation of local IRB approval from each PREMIER center should be sent to the Coordinating Center, along with approvals of subsequent changes. Periodically, the Coordinating Center will provide each PI with trial-wide information on adverse events for their IRB.

Provision of Medical Care to Participants

In the course of screening participants and conducting interventions, medical problems will occasionally be identified among participants. The responsibility of clinical centers in following up such problems will vary from site to site according to generally accepted medical guidelines, individual IRB requirements, and the resources available to provide referral and follow-up services. In no instances, however, should resources essential to the proper implementation of the Protocol be utilized to provide medical care services.

Disclosure of Study Results

Participants are told their baseline blood pressure measurements and also receive a summary of their six-month blood pressure measurements. Provision of such information is appropriate in view of the fact that many participants will have stage 1 hypertension. Participants also receive a complete set of blood pressure results, along with a summary of their laboratory measurements and information about the overall findings of the trial, at the conclusion of intervention. Participants are alerted if their blood pressure goes above a predetermined escape level at any point in the trial.

Confidential study data may be provided to a participant or health care provider on a need-to-know basis, if necessary for medical management or other safety concerns. This option is not disclosed to participants in advance. Clinics will notify the Coordinating Center of any participant who is unblinded to their blood pressure values during the intervention period.

PREMIER Investigators may share process data within their own departments at their own institutions. Otherwise, no PREMIER results may be presented until after the main outcomes paper is in press.

Publicity

Unpublished results derived from PREMIER data may not be discussed or released without authorization of the Steering Committee. The Publications Committee will recommend to the SC general guidelines for the content and timing of news releases and interviews for presentations and publications. PREMIER investigators may discuss design and recruitment issues with the media, but should inform the Steering Committee of any PREMIER-related information scheduled for release in the national media.

Access to Stored Laboratory Specimens

PREMIER will store a variety of frozen blood, urine, and buffy coat samples from PREMIER participants. Proposals to use these samples should be submitted to the PREMIER Steering Committee in writing. These proposals should include the type of study/test proposed, the amount of each sample required to conduct it, the rationale for the test, the study questions and hypotheses to be addressed, the plans for publication of the data, the approximate cost of the proposed test(s), and the source of funds to conduct them. Study investigators not involved in the initial proposal may request to be included in the working group conducting the additional studies.

The discussion of whether to permit use of the stored samples should include attention to possible alternative uses of limited materials. That is, the Steering Committee will attempt to plan for optimal uses of the stored samples rather than simply to grant requests for their use on the basis of which were submitted first. Use of stored specimens requires that an ancillary studies request be submitted.

Any analysis of biological specimens must be approved by each center's IRB.

Archiving of Source Documents and Biological Specimens

All source documents and biological specimens obtained during the conduct of PREMIER should be stored until the year 2007 or until the PC formally dissolves. Before any source documents or biological specimens are discarded, approval must be sought from the Steering Committee. Before disbanding, the Steering Committee will determine the future storage or disposal of source documents and stored biological specimens.

Summary of Edits

Changes between version 1.0 and 1.1:

- Updates text and figure 2.1 to show that manuscripts must only be annotated using results of data requests specific to the paper.

Changes between version 1.1and 1.2

- Minor edits to show that publications forms are available on the website

Publications

Scope of the Guidelines

This policy covers papers, abstracts, posters, and oral presentations that involve data collected as a part of the PREMIER study. These policies will remain in force until the Publications Committee (PC) is formally dissolved. The PC consists of each principal investigator or his/her designee and an NHLBI Project Scientist. Other PREMIER investigators may also participate.

Initiation of a Writing Project

Initiation of a writing project can begin in one of two ways:

1. A member of the PREMIER project may complete a Proposal for a PREMIER Paper (Form #400)
2. The SC or PC may also appoint a writing group to work on a specific publication.

To Propose a Paper

A member of the PREMIER project completes Form #400 (Proposal for a PREMIER Paper), which specifies the research question(s) and the primary variables to be used in the analysis. This form is available on the PREMIER website under "Forms".) The individual who completes this form is termed the "convener."

The convener, after adding known interested authors from his/her own or other site(s), transmits copies of the form to the Coordinating Center and to the PC Chair. The CC will circulate the proposals to the PC members for approval via PREMIER web site. Paper ballots may still be used in certain situations. As soon as the proposals are posted on the web site, PC members will be notified that a new proposal is ready for online voting. After reviewing Form #400 via PREMIER web site, PC members can then cast their vote. If a paper ballot is used, the CC circulates the Form #400 along with Form #401 (PC Review Form for a PREMIER paper) to the PC members for approval. PC members are responsible for circulating new paper proposals to investigators at his/her site and indicating on the ballot all interested co-authors.

Writing project proposals submitted to the PC must be reviewed promptly. PC members review the proposal, and vote online or sign and return the completed Form #401 to the CC within 14 days. Nonresponse is considered to be approval. PC members who are out of town can delegate responsibility for their vote.

Once the voting deadline is reached, the CC informs the convener and the PC Chair whether or not the proposed paper has been approved. If not approved, the PC Chair discusses questions or concerns raised by reviewers on the Form #401 with the convener. The convener responds to the PC Chair with a revised request or with a written response to the concerns, and sends a copy to the CC. The PC Chair decides if the response satisfies the concerns, or may defer approval until the PC can discuss the issues in a ***conference*** call***, via e-mail,*** or ***in a face-to-face*** meeting. The PC Chair notifies the CC whether or not proposed projects requiring discussion are approved.

The CC maintains and distributes a list of approved papers. Each approved paper is assigned a number and a short title that should be used on all correspondence related to the paper. See Figure 2.1 for an outline of the paper approval process.

Assigning Priorities

The PC, in conjunction with the SC, assigns a priority number from 1 to 3 to each paper indicating the importance of the proposed manuscript, with 1 being most important. The CC uses these priority scores to help prioritize the work it does in meeting analysis requests.

Forming a Writing Group

PIs are responsible to inform potential authors at their site of the formation of the writing group when the proposal is submitted. Interested investigators or the local PI should notify the convener. The CC also assigns a senior level statistician, who could be employed at the CC, one of the clinical sites, or the PO, to assist in the development and writing of each paper. This person will typically also be a co-author on the paper.

After approval, the convener sets up the first conference call or meeting of the writing group. At this first call/meeting, if a chair has not already been appointed, the writing group selects a chairperson from among its members. The chairperson serves as the first author on the paper, and is responsible for reporting progress on the paper to the CC at regular intervals.

The writing group chair notifies the CC that the group has convened and a chair has been selected, and also confirms the membership of the writing group. See Figure 2.1 for an outline of the writing group formation process. After formation, changes in the writing group (withdrawals or additions of members) are directed to the committee chair, who then notifies the CC. The current composition of each group is updated and posted on the PREMIER website by the CC. Membership can be changed only by the writing group chair.

Submission of Analysis Requests

All requests to the CC for statistical analysis should come directly from the writing group chair or the lead statistician on the project. The lead statistician should review all requests for appropriateness before analysis is begun. In all cases, requests should receive some level of appropriate statistical review prior to being assigned to a CC analyst. Exceptions may be made for simple requests such as descriptive tables not requiring analysis. All requests should be made using the Data Analysis Request Form (Form #403).

To facilitate manuscript preparation, the CC works with the lead author and the senior statistician to develop an analysis file for use with each approved paper. The Data Release Request Form (Form #404) is used to document the necessary information.

Copies of the analysis file are given to the lead statistician and to other members of the writing group who request a copy so that they can conduct their own preliminary analyses. The CC also

uses this file to fill data requests. The CC informs the investigators if the data in the analysis file have not been fully cleaned. All analyses made using preliminary data require subsequent verification before a manuscript can be approved for publication. If this verification is not conducted by the CC, a statement to this effect must be included in the METHODS section of the paper.

Once requests are submitted, the lead analyst at the CC assigns one or more staff analysts to work on various aspects of the request. The CC also sends a memo summarizing the request to the lead author to insure that it has correctly interpreted the request. The CC will not begin work on a data request until it receives confirmation from the requestor that the CC has correctly interpreted the request.

Each request is assigned a data request number that will be used on all subsequent communications related to the request. The CC often works on multiple, similar requests and uses the assigned number to avoid confusion. Some requests, due to their complexity or the nature of the programming tasks involved, may be operationally divided into several separate requests internally at the CC. When this occurs, each of these "requests" is treated according to the procedures outlined above.

The data request number should be left on all tables and figures that the CC generates until the final manuscript submission. This number should also be used to reference any numbers used in the text (i.e., in parentheses, following the text). This annotation allows the CC to efficiently return to the original output to verify the numbers in a table, figure, or text discussion as part of the manuscript verification process. Failure to use this data request number may add substantially to the verification time. If this number is missing, the CC will be unable to verify the manuscript and will return it to the author for the information to be added. Authors are advised to flag these and other data annotations as "hidden" text, so that they can be stored with subsequent iterations of the document and yet be conveniently turned on or off for purposes of viewing or printing.

See Figure 2.1 for an outline of the analysis request process.

Approval of Abstracts

Abstracts of PREMIER results intended for presentation at scientific meetings should be sent directly to members of the PC and to the Project Office along with a completed Form #405 (PREMIER Abstract Review Form), for approval prior to submission. A copy is also sent to the lead analyst at the CC for numbers verification. The sites and the CC must receive these abstracts at least five working days prior to the intended date of submission. Members of the PC and the Project Office must respond (using Form #405) within three working days of receipt of an abstract. Designated alternates may respond on behalf of PC members or Project Office representatives who are unavailable. Non-response within 3 days is considered approval. The CC must verify all numbers on the abstract prior to approving the abstract request.

Responses shall be sent directly to the PC Chair and the CC and shall indicate approval, disapproval, and any suggested/required edits. The PC Chair will notify the author and the CC when an abstract is approved. Abstracts may not be submitted for publication until the PC chair informs the requester that the abstract was approved.

Approval of Manuscripts

Prior to submission of manuscripts for approval, a copy of the annotated manuscript is submitted to the CC for verification of all numbers and figures, including those in the text, by the analyst staff. Once the numbers and figures have been verified and any needed corrections have been made, the manuscript can be submitted for approval. Manuscripts not verified by the CC shall explicitly state this in the METHODS section.

A copy of the manuscript and a completed Manuscript Review Form (Form #406) should be sent to the Coordinating Center, which in turn forwards two copies to the NHLBI Project Scientist and one copy to each member of the PC for review. The NHLBI Project Scientist submits the manuscript for NHLBI internal review, which can require up to six weeks. All manuscripts must be received by NHLBI. NHLBI approval is required only if there is an NHLBI author. Although PC approval and Project Office approval may be requested simultaneously, the PC chair may require a second PC review if the Project Office recommends substantive revisions.

The members of the PC must respond in writing (using Form #406, PREMIER Manuscript Review Form) within 30 days of receipt of the manuscript to the PC Chair, who will relay comments to the chairperson of the writing group and to the coordinating center. Designated alternates can respond on behalf of PC members who are out of town. Non-response by a PC member is assumed to be an approval.

The PC resolves conflicts over the acceptability of manuscripts. If a consensus cannot be reached, then a majority vote of the committee resolves the issue. Authors can appeal any such decision to the Steering Committee. The PC may withdraw, by majority vote, any manuscript after it has been submitted and before it is published.

See Figure 2.1 for an outline of the manuscript approval process.

Acceptance of Abstracts and Manuscripts

The main author sends a copy of the submitted abstract and submitted manuscript to the CC, and, if further revisions were made to the manuscript, a copy of the final version. It is the responsibility of the first author of any manuscript, abstract, or presentation to notify the PC Chair and the CC of the acceptance or rejection of the paper, abstract, or presentation. After publication, the main author shall send to the CC seven copies and the appropriate citation for any published abstract and seven reprints and the citation for any published manuscript. The CC will store copies of all scientific manuscripts both for ancillary and for full study papers and abstracts, and will distribute a copy of the published abstract or manuscript to each PI and the Project Office. It is the responsibility of individual PIs to distribute copies of abstracts and

manuscripts to other investigators at their sites. The CC distributes regular reports of publications and presentations. Investigators are encouraged to share copies of slides and handouts. Hard or electronic copies of data slides and handouts to be presented at national meetings should also be circulated to the PC Chair and the CC for distribution to other PREMIER investigators. The coordinating center maintains copies of all the slides it receives, and makes them available to other investigators upon request.

Figure 2.1: Outline of PREMIER Process for Producing a Paper

Approval
PREMIER investigator proposes paper
PC members review proposal, inform potential authors at their site, and vote
CC notifies convener and PC chair of outcome
CC assigns statistician
↓
Writing Group Formation / Exploratory Analyses
Convener works with assigned statistician to prepare for first call
Writing group convened, writing group identifies chair; Writing group chair informs CC of group membership/chair
Writing group chair works with assigned statistician on exploratory analyses
Writing group chair and assigned statistician generate formal analysis requests
↓
Analysis Requests
Requests sent to CC Lead Analyst; Analyst is assigned to each request
Analyses completed and reviewed; Results or data release sent to writing group chair
↓
First Draft
Writing group reconvened
Chair prepares outline of manuscript and distributes writing assignments
First draft completed and circulated for review
↓
Subsequent Drafts
In consultation with assigned statistician, additional analyses may be specified
Requests sent to CC Lead Analyst; Analyst is assigned to each request
Analyses completed and reviewed; Results or data release sent to writing group chair
Manuscript draft recirculated to writing group.
↓
Review
Annotated manuscript submitted to Lead Analyst at CC for numbers verification
Note: Annotate using data requests specific to the paper; do not use results other than from data requests specific to the manuscript to annotate
Manuscript submitted to PC for approval
Manuscript submitted to NHLBI for review (or approval if NHLBI author on paper)
Final revisions made
↓
Submitted to Journal
Manuscript submitted for publication; author supplies CC with copy of submitted manuscript
Author notifies PC Chair and CC of acceptance or rejection of manuscript
↓
Paper Published
Author supplies CC with 7 copies of the published manuscript;
CC distributes copy of published manuscript to PIs and Program Office

These items are paper milestones that are reported in the PREMIER Paper Milestones Report. The writing group chair is responsible for updating the CC on the progress of a paper through each its milestones.

Authorship

Authors who participate in the writing of a manuscript from the PREMIER project do so in accordance with the International Committee of Medical Journal Editors guidelines (*N Engl J Med* 1991;324:424-8)(see Appendix 2.1). First authors are expected to delete names from the final list of authors if those individuals have not participated in the writing and/or analysis of the paper in accordance with those guidelines. Unless prohibited by journal policy, all papers (excluding those resulting from ancillary studies) should include the words "PREMIER Research Group" in the authorship line, even if the analyses were not done by the CC. If analyses were done locally and not checked by the CC, a note must be added stating that analyses were done locally., e.g. "all analyses were conducted locally and have not been verified by the Coordinating Center." The SC may allow exceptions to this policy. All papers should also include an "Acknowledgments" section that lists the PREMIER investigators and key staff at the Clinical and Coordinating Centers and Project Office unless journal policy prohibits publication of such a list. In general, at least one representative from each participating institution (i.e., Clinical Centers, Coordinating Center, and Project Office) should be included as an author on papers using study-wide PREMIER data. However, membership from each site is not required.

First authors will usually be PREMIER investigators or individuals who are substantively involved in the design or conduct of the study. Others may serve as first authors if:

- the opportunity of first authorship on a project has been offered to all PREMIER investigators and none requested to serve as first author,
- at least one other PREMIER investigator serves as a co-author and "sponsor" of the project, and
- the fellow or scientist has played a major role in the data analysis and writing for the paper.

First authorship is decided by the writing group at its initial meeting and will typically be the convener. The first author also serves as Chair of the writing group. Conflicts about first authorship should be resolved, if at all possible, by members of the writing group. In case the writing group is unable to resolve a conflict, the PC will adjudicate and may assign first authorship. This assignment may be appealed to the SC.

If progress on a given writing project is unduly slow, the PC may request an explanation from the chair of the writing group or the lead statistician, depending on the source of the delay. If timely progress is not likely to occur in the near future, the PC may, at its discretion, assign a new Chair to the writing group, or may ask the CC to increase the priority rating of the paper. Such action may be appealed to the Steering Committee.

The first author should determine the order of co-authorship on a paper. In general, authors will appear in order of contribution to the writing and analysis of the paper. When contributions to writing and analysis have been similar, priority should be given to:

- those who have contributed to a greater degree to the design and implementation of the trial,
- balance across centers, and

- junior investigators.

If the writing group cannot resolve conflicts regarding the order of authorship, the PC will adjudicate and may assign the order.

Ancillary Studies

All studies of participants enrolled in the PREMIER project that are not part of the main protocol, including proposals to analyze stored specimens, must be approved by the Design and Analysis Committee (D&A) prior to enrolling participants and collecting data. In order to obtain approval, the investigator wishing to do an ancillary study must complete and submit the Ancillary Study Request Form (Form #402) to the CC for circulation to the D&A Committee. **PIs are responsible for ensuring IRB approval for ancillary studies at their site. If a proposal is subsequently submitted for IRB approval, copy of the final approval letter from your IRB must be sent to the CC, which maintains a centralized file of all such approvals for archival purposes.** The D&A reviews the proposal within two weeks. The primary purpose of this review is to ensure that the ancillary study will not interfere with recruitment, intervention or data collection for the main study. The D&A may make suggestions for modification in order to assure that the ancillary study meets the non-interference criterion. The D&A may refuse to approve ancillary projects that appear to interfere with conduct of the main trial.

All ancillary studies approved by D&A must then be approved by the Steering Committee. The CC maintains a listing of approved ancillary studies and periodically provides a copy to the DSMB. Once the ancillary study has been approved, oversights of publications resulting from it are the responsibility of the Publications Committee.

For papers resulting from ancillary studies, the following statement, or its equivalent, should be inserted in the Methods section of the paper:

"This was a study ancillary to the PREMIER study and, as such, was designed, conducted, and analyzed by the co-authors only ."

Papers resulting from ancillary studies should acknowledge the PREMIER research group and participants by including the following statement, or its equivalent, in the acknowledgement section. Acknowledgement of specific individuals, groups, or committees may also be appropriate. The local PI will adjudicate disagreements over authorship.

"The authors are extraordinarily appreciative of the PREMIER participants and of the entire PREMIER Research Group, which included investigators and staff from the Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, MD; the Kaiser Permanente Center for Health Research, Portland, OR; Duke University Medical Center, Durham, NC; Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA; and The Johns Hopkins Medical Institutions, Baltimore, MD.

No abstracts from PREMIER ancillary studies that include post-randomization data may be submitted until the main outcomes abstract has been presented. Papers for PREMIER ancillary

studies may not be submitted until the main outcome paper for PREMIER has been accepted for publication.

Paper Monitoring

The CC notifies the requestor of the projected number of hours and timeline for completion of all data requests. The CC also supplies regular reports to PREMIER investigators as to the status of requests, and progress of individual papers. It is recognized that timelines may change from initial estimates due to unanticipated difficulties or competition from requests with higher priorities.

Release of Data for Public Access

At the end of the trial, the CC supplies each PI and the PO with a clean copy of the study data along with appropriate documentation in electronic form. The Project Office is responsible for making the dataset available to the general public under the terms of the Freedom of Information Act.

Appendix 1 Authorship

Excerpt from "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," from The New England Journal of Medicine, 324(6):424-428, 1991.

All persons designated as authors should qualify for authorship. The order of authorship should be a joint decision of the co-authors. Each author should have participated sufficiently in the work to take public responsibility for the content.

Authorship credit should be based only on substantial contributions to (a) conception and design, or analysis and interpretations of data; and to (b) drafting the article or revising it critically for important intellectual content; and on (c) final approval of the version to be published. Conditions (a), (b), and (c) must all be met. Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is also not sufficient for authorship. Any part of an article critical to its main conclusions must be the responsibility of at least one author.

A paper with corporate (collective) authorship must specify the key persons responsible for the article; others contributing to the work should be recognized separately (see Acknowledgments).

Editors may require authors to justify the assignment of authorship.

Summary of Edits

New Changes in Version 1.1

- Added description of national recruitment website.

3. Trial Communications

Importance of Trialwide Communications

Maintaining lines of good communication is important to the successful operation of a long-term collaborative clinical trial. During the course of the PREMIER study the coordinating center will be responsible for the following tasks that depend heavily on effective communication channels and skills:

1. Arranging orientation and initial training of clinical center personnel
2. Monitoring project adherence
3. Reporting to the Project Office, committees, and DSMB
4. Responding to clinical center and Project Office requests,
5. Staffing trial committees, including logistic arrangements and distribution of meeting minutes

The tools of communications for PREMIER include: regular meetings of the Steering Committee and its subcommittees, conference calls, website and site workstation posting of study documents, e-mail, sequential memos, telephone calls, data edit reports, and routine trial monitoring reports.

This section summarizes the principles for PREMIER communications and describes the procedures for sending communications between participating institutions.

Principles of PREMIER Communications

Electronic Communications

A key component of the PREMIER communications protocol is that wherever possible, documents will be delivered electronically. The coordinating center will use e-mail and the PREMIER web site as the preferred delivery method for all study materials.

Direct Delivery of Urgent Items

Urgent communications (faxes and express mail) are normally sent directly to the recipient, rather than the contact person, to avoid any delays in delivery. However, if a staff member is out of town, the contact person is responsible for ensuring that their mail and incoming faxes are checked and re-routed if necessary.

E-mail messages are also normally sent directly to the addressee, rather than to the contact person. If the message requires urgent follow up, then the sender should copy the contact person so that the message will be handled even if the recipient is out of town or unable to check their e-mail. Some project staff do not have reliable e-mail access, so urgent information will be sent to them via fax or express mail.

Central Contact Person for Non-Urgent Items

For non-urgent documents and materials, each participating institution identifies a single person who serves as the contact person for that site. PREMIER communications directed to several people at a site should be sent to the contact person, who is then responsible for forwarding copies of the document as appropriate. In the event that this individual is not available, backup coverage is arranged at the clinical site so that someone else checks for incoming correspondence on a daily basis.

Rapid Turnaround of Minutes

Especially during the initial planning stages of a trial, the work of the trial is done by committees who meet to design the trial and work out the various procedures. For this process to proceed smoothly, it is critical that accurate minutes of committee meetings be taken and that they be distributed in a timely manner. The coordinating center takes notes during all PREMIER committee meetings and conference calls. If a non-coordinating center person takes minutes for a meeting, it is their responsibility to forward the minutes to the coordinating center secretary. Meeting minutes are posted weekly on the PREMIER website.

Rapid Turnaround of Queries

All participating institutions in the trial shall make every effort to promptly respond to queries. Phone messages, e-mail messages, or written queries should be answered within a maximum of five working days.

Elements of Communications Network

The coordinating center uses a variety of tools to facilitate study communications.

Internal Web Site

The coordinating center will use the PREMIER web site as the primary study communications tool. This allows maximum access to all study materials by all project staff, regardless of geographic location. While most of the documents on the site originate with the coordinating center, committee chairs can also submit documents to be posted on the web site. The web site is secured so that only project staff will have access.

National Recruitment Website

The coordinating center also maintains a website that is accessible to potential enrollees. It will convey general information about the study, including contact numbers for recruitment at each site.

Fax and Mail Delivery

For informal communications, and all documents that can not be posted to the web site, the coordinating center and sites use a combination of fax, e-mail, express mail, and regular mail to send written study communications and materials.

Site Computer Workstations

After the study is underway, an additional communications tool will be available. Each of the clinical centers will have a computer workstation on site as part of the PREMIER data management system. The workstation transmits study data to the coordinating center, and receives electronic copies of MOP chapters, forms, the protocol, and staff directories from the coordinating center. The clinical centers will also have a printer for their workstation, so that they can print master copies of these study documents in a consistent manner.

Selection of Communication Method

The coordinating center maintains a detailed document, the "Communications Flowsheet," that describes which methods should be used for each type of communication. This ensures consistent, reliable, and efficient communications with all project staff.

The appropriate communication method is selected based on the information to be communicated, its format, the urgency of the message, the amount of information to be sent, and the location of the recipient.

The following table is a summarized version of the Communications Flowsheet:

Communication Method	**When To Use**
E-mail*	Informal communications, notifications of web postings, notifications of revisions to study documents on web/workstations
Phone	Informal communications
Web Site*	Minutes; packets of materials for committees to review; draft and final MOP chapters, forms, protocol; staff directory; conference call schedule; analysis guide; paper proposal and manuscript review materials/ballots
Fax	Short memos, short trial monitoring reports
Express Mail	Long memos, long trial monitoring reports, urgent supplies/materials, urgent bound reports/documents.
US Mail	Non-urgent supplies/materials, non-urgent bound reports/documents
Site Workstation Posting	Final MOP chapters, forms, protocol; staff directory

**Note: express mail or fax delivery may be used in cases of e-mail failure, or inability to access the web site.*

Summary of Edits

Summary of changes between version 1.0 and version 1.1

- Baton Rouge consent description updated to reflect that the second consent, covering part of screening and all activities following randomization, is obtained at SV2.

4. Human Subjects

To participate in PREMIER, participants must provide written informed consent using procedures reviewed and approved by each clinical center's local IRB. This consent should cover screening visits, interim measures, and intervention. The number and timing of these consents are determined by the local IRBs and may vary across the clinical centers. At a minimum, an initial consent is obtained prior to commencing the SV1 visit to cover screening activities and baseline measurements, and a separate consent is obtained after SV3 and prior to randomization to cover intervention measurements and activities.

Information leading to informed consent must be provided in a language that is understandable to the participant. Even when extensive printed information is provided, the investigator or interviewer must verify that the participant understands what he/she has read and heard. The participant must be given the opportunity to ask questions, and the interviewer should ask questions to determine the participant's level of understanding.

Summary descriptions of each clinical center's consent procedures are included as part of this chapter.

Principles of Informed Consent

In seeking informed consent, the following information should be provided to each participant:

1. A statement that the study involves research, an explanation of the purpose of the research, the expected duration of the individual's participation, a description of the procedures, and identification of any experimental procedures.
2. A description of any reasonably foreseeable risks or discomforts to the participants.
3. A description of any benefits to the participants (or to others) that may reasonably be expected from the research.
4. A statement describing the extent to which confidentiality of records identifying the participant is maintained.
5. An explanation as to whether any compensation or medical intervention is available if injury occurs and, if so, what it consists of, or where further information may be obtained.
6. An explanation of whom to contact for answers to pertinent questions about the research and the participant's rights, and whom to contact in the event of a research-related injury to the participant.
7. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant may otherwise be entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant may otherwise be entitled.

8. Anticipated circumstances under which the individual's participation may be terminated by the investigator without regard to the individual's consent.

Process of Obtaining Informed Consent

Various studies indicate that the circumstances under which consent is obtained in clinical trials can have a profound influence on the participant's interpretation of information communicated during the consent discussion and on the freedom of participants to make their own decision. All clinical centers will therefore follow the guidelines listed below when obtaining informed consent.

1. Participants should have adequate time to evaluate the pros and cons of participation. Allow the participant to take the consent form home to review if necessary.
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).
3. To be eligible for participation in the study, participants must have the capacity to give their own consent. If a participant is incapable of understanding what is expected of him or her as a participant in the study, it is not permissible to obtain informed consent from a guardian. The study requires daily responsibilities that cannot be easily assumed by other persons.
4. The setting in which the consent is obtained should be as private as possible so participants can freely ask questions without embarrassment.
5. To avoid pressuring the participant only one person associated with the study should be present when the participant reviews the consent form. Additional staff may be present for other purposes, such as training, if participant permission is obtained.
6. The participant should be given a copy of the consent form after it is signed and witnessed.
7. Participants should be encouraged to keep the consent form because it contains useful information about the study that they can review from time to time.
8. In situations where the person or organization responsible for obtaining the participant's consent is also involved in that participant's regular medical care, the participant must be told in no uncertain terms that they will be treated with the same degree of interest and concern regardless of whether or not they participate in the study. It is desirable, therefore, that someone other than the participant's health care provider be the person responsible for obtaining the informed consent.

Summary of Site-Specific Consent Procedures

This section contains a brief summary of the process for obtaining informed consent at each site.

Baltimore

Consent for PREMIER volunteers at Johns Hopkins ProHealth occurs in two stages. Screening consent is obtained at SV1 and covers all aspects of screening, including data collection conducted at the R/I visit prior to the randomization event. Randomization consent occurs no sooner than the end of SV3 and covers all participant activities that occur following randomization.

Baton Rouge

Consent for PREMIER participants at the Pennington Biomedical Research Center occurs in two stages. At SV1, all participants sign an informed consent that covers all aspects of PREMIER screening. This consent also includes consent for a battery of phlebotomy, body composition, and other evaluations that are performed on all participants receiving evaluations for any study at the Pennington Center. A second consent is obtained at SV2, and covers all participant activities that occur for the rest of screening and all activities that occur following randomization.

Portland

Consent for PREMIER volunteers at the Portland clinical site will be obtained four times; at each of the three screening visits, and at the R/I visit. Each of the three screening visit consents will cover all aspects of that individual visit. In addition, the SV3 consent will include the activities at the interim visit. The randomization consent will be obtained at the beginning of the R/I visit, and covers all participant activities that occur during the R/I visit and following randomization.

Durham

Consent for PREMIER volunteers at the Duke clinical site is obtained twice. The first consent covers all screening activities and is obtained at the SV1 visit. The second consent is obtained at the randomization visit and covers all participant activities that occur following randomization.

Assurance of Informed Consent

The CC receives a blank copy of all consent documents used at each site as well as copies of each site's IRB assurances forms. In addition, during site visits the CC verifies properly signed consent documents on a random subset of participants.

Confidentiality

All participant information, including the fact that an individual is participating in the study, is considered confidential. This confidentiality is assured in PREMIER through several

mechanisms. First, each participant is assigned an anonymous study ID, which is then used on all study forms. Only where absolutely necessary to assure data integrity is a participant's name also included on study forms.

Second, all study forms, biological specimens, and paper records that contain participant information (e.g., address lists, phone lists) are kept in secured, locked areas when not in use. In addition, such materials, when in use, are kept away from public scrutiny. Materials and specimens that need to be discarded are destroyed.

Third, access to all participant data and information, including laboratory specimens, is restricted to authorized personnel. In the case of computerized data, this restricted access is assured in several ways. At the clinical centers, the data are maintained on stand-alone personal computers (PCs) that are not networked to any other PC. Further, access to the study data on these machines is password protected. Staff members receive individualized account numbers and passwords that allow them access only to those elements of the data management system to which they are authorized. At the Coordinating Center, access to computerized data is restricted in two ways. First, only authorized personnel are granted access to the data, and, second, this access is further restricted by password protection. In addition, Coordinating Center personnel are annually required to sign a confidentiality statement affirming that they agree to abide by the Center for Health Research's policies on research confidentiality and ethics.

When the study database is made available to clinical centers, to the Project Office, and, ultimately, to the public, it will not include actual identities and contact information for participants. Such information is retained under lock and key at the individual clinical centers and at the Coordinating Center for use in the event that future follow-up of the study participants is necessary.

Finally, participants are not identified by name in any reports or publications, nor are data presented in such a way that the identity of individual participants can be inferred.

Data Integrity

Data maintained at the clinical centers are internally backed up each day onto a second hard drive located in the PC. Copies of the master database maintained at the Coordinating Center are backed up daily and archived off-line on a daily, weekly, monthly, and yearly basis.

Risks

The PREMIER eligibility criteria are designed to exclude those individuals at undue risk for cardiac events or for whom the PREMIER interventions would be inappropriate. Wherever feasible, we have followed national guidelines in determining these criteria. We have also followed national guidelines in setting our blood pressure escape monitoring criteria, and all

participants meeting escape thresholds are referred to a physician for further evaluation. If these escape thresholds are met prior to randomization, the participant is also excluded from participating in PREMIER.

As a result of these safeguards, the PREMIER study should not pose any major health risk to participants. The most likely physical health risks associated with participation are gastrointestinal upset (e.g., bloating), increased frequency and bulk of stools (resulting from the high fiber content associated with adherence to some of the study dietary recommendations), minor discomfort from the venipunctures, and possible increase in minor injuries (muscle strains, sprains, etc) associated with the adoption of a physical activity regimen. These effects are either transient or readily reversible when intervention procedures are stopped. Participants are monitored for reactions to study procedures and these procedures can be terminated if necessary.

Additional risks and inconveniences to study participants include: accidental breach of confidentiality; the inconvenience of having to come to clinic or counseling sessions on a frequent basis; the inconvenience of collecting 24-hour urine specimens; and the inconvenience of receiving data collection interviews via the telephone within specified time windows.

The PREMIER protocol also provides for regular monitoring of participants for other adverse health outcomes, and all adverse outcomes are routinely reported to the trial's Data and Safety Monitoring Board, which may propose termination or modification of the study if it determines that participants in any of the intervention groups are being placed at undue risk through their participation in PREMIER.

Benefits

The benefits associated with participation in the study include: counseling for positive health related behavior change, regular blood pressure monitoring, cash reimbursement (amounts vary by center and may not be provided at all centers), and free laboratory tests that have a small possibility for early diagnosis of an illness. Participants also have the satisfaction of participating in a clinical trial with potentially major public health implications.

Based on the results of earlier behavioral research, we anticipate that a majority of participants randomized to the active interventions will experience a reduction in blood pressure while participating in PREMIER. Moreover, we anticipate that those participants in the weight loss component of the active interventions will lose a significant amount of weight. We also anticipate an increase in regular physical activity and a resulting improvement in fitness measures among those in the active interventions. Even participants randomized to the advice group will receive, over the course of the 18-month follow-up period, three one-hour individual counseling sessions to discuss lifestyle change strategies and options.

Gender and Minorities

The PREMIER study will recruit a population that is 40% African American and 50% female. Recruitment of minorities and women is formally monitored quarterly and reports forwarded to NHLBI. Minorities other than Blacks are also eligible to participate, although no targets are set for these categories. Further, we have specifically designed the study to have good power to detect effects on the primary study endpoints for race and gender subgroups.

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Changed p.5 text “high normal BP and borderline HTN” to “above optimal BP and stage 1 HTN”
- Added statement that personal physicians of all participants eligible for randomization are sent a letter describing the trial and asking them to contact the site if they have any questions or concerns about their patient’s participation in PREMIER.

5. Recruitment

Study Population

Study participants (n = 800) will be 25 years of age or older, with systolic BP of 120-159 mmHg and diastolic BP of 80-95 mmHg. Approximately 400 (50%) of the participants will be female, 320 (40%) will be African-American, and 240 (30%) will have stage 1 hypertension. After three screening visits, participants will be randomly assigned to one of the two lifestyle behavioral interventions or a group that receives advice. Follow-up will last 18 months after randomization. The primary outcome variable is systolic BP (SBP). Other outcomes include diastolic BP (DBP), adherence to dietary and physical activity regimens, and the onset of hypertension.

Eligibility Criteria

The eligibility criteria for this trial (Table 2) have been selected to yield a reasonably representative sample of adults with above optimal BP and stage 1 hypertension. Most of these criteria exclude individuals for whom the interventions would be inappropriate, or those who have health problems requiring immediate attention. Inclusion and exclusion criteria are defined in detail below:

Contact with Personal Physicians

In addition to the requirement for physician notification for a positive Rose questionnaire in order to determine study eligibility, clinical center staff must notify the personal physician of otherwise eligible study candidates to see if she has any concerns about her patient's participation. This notification can be in the form of a fax-back request for concerns, if any. A positive response from the provider is not required in order to randomize the participant. The absence of a negative response is sufficient. In the event that the study candidate does not have a personal physician, has a negative Rose questionnaire, and is otherwise eligible to participate, no further action is required.

Table 2. Eligibility Criteria

Inclusion Criteria

Baseline SBP 120-159 mmHg and DBP 80-95 mmHg
Age 25 or older as of the PSV visit
Willing and able to participate fully in all aspects of the intervention
Provide informed consent
BMI 18.5-45 kg/m^2
Access to telephone

Medication Exclusions

Regular use of antihypertensive drugs or other drugs that raise or lower BP (any in previous three months prior to SV1)
Current use of insulin or oral hypoglycemic agents
Use of oral corticosteroids >5 days/month on average
Current use of medications for treatment of psychosis or manic-depressive illness
Use of oral breathing medications other than inhalers > 5 days/month on average
Use of weight-loss medications in the 3 months prior to SV1

Medical History Exclusions

Cardiovascular event (stroke, MI, PTCA, CABG, or ASCVD-related therapeutic procedure)
Congestive heart failure
Current symptoms of angina or peripheral vascular disease by Rose Questionnaire (Rose et al., 1977), unless approved by both participant's personal physician and a PREMIER clinician. If no personal physician, must be referred.
Cancer diagnosis (except for non-melanoma skin cancer) or treatment in past two years
Renal insufficiency (GFR<60 ml/min as estimated using Cockroft-Gault formula)
Random glucose $\geq$ 160mg/dL or FBS $\geq$ 126 mg/dL
Psychiatric hospitalization within the last 2 years

Other Exclusions

Unable to provide acceptable BP measurements
Consumption of more than 21 alcoholic drinks per week
Consumption of 6 or more drinks on one occasion twice or more per week
Planning to leave the area prior to the anticipated end of participation
Body weight change > 15 pounds in the 3 months prior to SV1
Pregnant, breast feeding, or planning pregnancy prior to the end of participation
Current participation in another clinical trial
Investigator discretion for safety or adherence reasons
Household member of another PREMIER participant or of a PREMIER staff member

Inclusion Criteria

- SBP 120–159 mm Hg and DBP 80-95 mm Hg

  Two blood pressure measurements are taken at each of the first three formal screening visits (SV1, SV2, and SV3), and the average of these six measurements must fall within the stated limits for both SBP and DBP. An additional set of measurements is taken at a later visit; however, this set does not determine eligibility.

Table 3. PREMIER Blood Pressure Eligibility Criteria

Visit	Measure	Eligible Range (mm/Hg)*
SV1	SBP	118-170
	DBP	78-100
SV2	SBP	119-165
	DBP	79-98
SV3	SBP	120-159
	DBP	80-95

*Cumulative average of SV measurements (see measures section)

  In order to identify participants not likely to meet these limits, somewhat wider eligibility limits are also established for the average cumulative blood pressures at each of SV1 and SV2 (see MOP Chapters 7 and 8).

  Participants who are excluded from the screening process because of blood pressure may re-start the screening process at a later date, but only as part of screening for a separate cohort.

- Age $\geq$ 25 years

  Participants must be 25 years of age or older at the prescreening visit. This is assessed by asking, at the prescreening visit, whether the participant is currently 25 years of age or older. Date of birth is also collected for confirmation.

- Willing and able to participate fully in all aspects of the intervention

  The staff repeatedly emphasize this issue with potential participants. A participant's willingness to complete the extensive battery of screening tests and visits is an indication of their overall commitment to the project and possibly their willingness to make lifestyle changes. Since next to blood pressure limits, this is likely to account for the majority of study exclusions, it is imperative that participants understand the nature and demands of the study as early into the screening process as possible.

- Body mass index 18.5-45 Kg/m^2

  The weight screening criteria have been selected to exclude those who are seriously underweight (they may not respond well to the dietary change interventions) and those who are massively obese.

- Willing and able to provide written informed consent

  In order to participate in the study, all subjects must provide written informed consent using procedures that are reviewed and approved by each center's local IRB. Typically, this will involve separate consent forms prior to screening and again prior to randomization.

- Easy access to telephone

  Participants must have easy access to a telephone in order to complete telephone diet recalls, and for other study-related contacts.

Exclusion Criteria

Medication Exclusions: use of any of the following:

Unless noted otherwise, current medication use is defined as any use within 21 days of the PSV visit or at any time thereafter. All participants are expected to bring their medication bottles to the SV2 visit for review by a clinic staff member.

"Unstable doses" of medications are operationally defined by the participant having either started, stopped, or changed the dosage of these medications during the past six months, except where noted below

- Antihypertensive drugs, and other drugs that raise or lower BP
  Defined as any use in 3 months prior to SV1

- Current use of any of the following:
  - Insulin or oral hypoglycemic agents
  - Oral corticosteroids (> 5 days/month on average)
  - Medications for treatment of psychosis or manic-depressive illness
  - Oral breathing medications other than inhalers (> 5 days/month on average)

- Weight loss medications
  Defined as use in the 3 months prior to SV1.

The Eligibility Questionnaire (Form #4) and the Medication Use Questionnaire (Form #11) contain lists of medications in each of these categories of excluded medications. In addition to these medications that are <u>not</u> allowed, the Medications Allowed During PREMIER Form (#102)

lists other medications that are approved for treatment of constipation, indigestion, and other minor conditions.

Medical History Exclusions:

- Cardiovascular event, congestive heart failure, angina, or peripheral vascular disease

  Participants are excluded if they report a prior CVD event (defined as stroke, heart attack, balloon angioplasty, bypass operation, or other vascular procedure) or if they report a clinical diagnosis of congestive heart failure. Confirmation is not necessary unless the participant is uncertain of the diagnosis and the clinical center still wishes to include him/her. A Rose Questionnaire for angina and peripheral vascular disease will be used to identify persons with these conditions. Because of the possibility of false positive tests, persons with a positive Rose Questionnaire can be enrolled if they have had a negative stress test within the past 6 months and both their physician and a study physician agree to let the person in the study.

- Cancer diagnosis (except non-melanoma skin cancer) within the past 2 years

  Participants are excluded if they report a prior diagnosis of cancer (other than non-melanoma skin cancer) within 2 years prior to SV1. The diagnosis of cancer and the status of therapy are based on the participant's self-report and do not need to be confirmed with the participant's physician unless a question exists about whether the cancer is currently active. Participants currently on cancer chemotherapy or with evidence of active malignancy or radiation therapy within the past two years are excluded.

- Renal insufficiency

  If the serum creatinine level is >1.5 mg/dL (men) or > 1.2 mg/dL (women) AND the calculated GFR is < 60 ml/min, the participant is ineligible. The GFR is calculated using the Cockcrault-Gault formula as listed below:

  Men: GFR = [(Wt in Kg)*(140-Age in years)] / [72* serum creatinine in mg/dl]

  Women: GFR = 0.85 * [(Wt in Kg) * (140-Age in yrs)] / [72* serum creatinine in mg/dl]

- Diabetes

  Defined as either nonfasting or random glucose ≥ 160 mg/dL or fasting blood sugar ≥ 126 mg/dL. Repeat testing to confirm the diagnosis may include either a non-fasting or fasting blood sugar.

- Psychiatric hospitalization within the last 2 years

  Defined as psychiatric hospitalization within 2 years prior to SV1

Other Exclusions:

- Unable to provide acceptable blood pressure measurements

  As detailed in MOP Chapter 17, individuals for whom valid and reliable measurements of blood pressure cannot be obtained are excluded from participation in the trial. This criterion applies only to blood pressure measurements taken with a random zero sphygmomanometer.

- Consumption of more than 21 alcoholic drinks per week and/or consumption of 6 or more drinks on one occasion twice or more per week

  This is determined at the prescreening visit and confirmed subsequently as part of the Eligibility Review that takes place between SV1 and SV2. In both cases the information is based on self-report. One drink of alcohol is defined as one can or bottle of beer, one glass of wine, or one shot of liquor.

- Planning to leave the area prior to the anticipated end of participation

- Body weight change >15 pounds in the 3 months prior to SV1

  This is determined by self-report.

- Pregnant, breast feeding, or planning pregnancy prior to the anticipated end of participation (women only)

  Any woman who is pregnant or trying to conceive a child at the time of the prescreening visit is excluded from the study, as are women who are breast feeding at the time of the prescreening visit .

- Current participation in another clinical trial

- Investigator discretion for safety or adherence reasons

  In addition to the trial's mandatory blood pressure escape levels, individual centers always have the option of excluding participants for reasons of safety as determined locally. At any time prior to randomization, each clinical center has the option of excluding participants for noncompliance with the study protocol. Noncompliance may include, for example, repeated no-shows or reschedules for clinic visits, poor attitude, or any other aspect of the participant's behavior that would suggest he/she is a poor candidate for the trial.

- PREMIER staff or household member of PREMIER staff

Overview of Recruitment

Each PREMIER clinical center recruits its participants in four separate cohorts. Specific recruitment approaches include: 1) targeted mailings to specific groups (e.g., employees of local industries, previous screenees), 2) mass mailings (e.g., vis-à-vis inserts in coupon packs and brochures to registered voters or licensed drivers), 3) community and worksite screenings, 4) mass media advertising (e.g., radio and television advertisements and public service announcements), and 5) electronic mail (e.g., to lists of employees) or Web site advertisement. Other approaches can be used, as long as the local IRB approves the new strategy.

Each clinical center has a recruitment coordinator who oversees recruitment efforts and who serves on the recruitment subcommittee. The recruitment coordinator is the primary liaison with the coordinating center for issues related to recruitment.

The coordinating center monitors recruitment activities and facilitates recruitment efforts by providing regular recruitment reports, organizing meetings and conference calls, and distributing meeting/call minutes. In addition to these regular trial monitoring reports, the coordinating center will develop additional reports (either on a regular or ad hoc basis) as requested by the recruitment committee or by the Data and Safety Monitoring Board. The coordinating center also facilitates, where appropriate, the preparation of recruitment materials for common use at the clinical sites.

Record Keeping

Other than for basic demographic information (e.g., gender and race), data collected at PSV are not considered study data and are not incorporated into the study database. The demographic data are entered only for participants who are eligible for SV1 and who remain interested. Individual clinical centers wishing to track demographic data on all participants will have to create their own system for entering data on ineligible PSV visits.

Beginning with SV1, all data collected on prospective eligible participants must be entered into the data management system. Data for all subjects who become ineligible must be entered up to the point at which they are identified as ineligible. All subjects who drop out of screening, become ineligible, or who are otherwise lost to follow-up must be formally closed out.

Summary of Edits

6. Prescreening Visit (PSV)

Overview

In order to be randomized, participants must complete a series of screening visits. Each screening visit includes questions and procedures designed to determine eligibility for the trial.

The PSV is intended as a fast, efficient way to identify ineligible participants prior to scheduling them for a formal screening visit. In addition, clinical centers have the option of obtaining a single, non-RZ blood pressure measurement as part of the prescreen. Individuals who complete the PSV are either excluded from further participation or are scheduled for screening visit #1 (SV1), which may occur concurrently with the PSV.

If more than 4 months elapse between the PSV and SV1, the PSV must be repeated.

Setting

The PSV may take place at the clinical center (e.g., coincident with the initial screening visit), via telephone, or at a location in the community convenient to the population being recruited. If the PSV is being conducted at an off-site location, the clinic staff need to make sure that adequate space and facilities (e.g., tables and chairs) are available to accommodate the participant flow and to assure privacy for the participants when answering questions.

Preparations for Prescreening Visit

The following materials are needed to conduct the prescreening visit:

- Informed consent form for PSV (if required by local IRB, see Chapter 04)
- Standard (non-RZ) sphygmomanometer and stethoscope (optional)
- Prescreen Eligibility Form (Form #1)
- PSV BMI Reference Chart (included with the instructions for Form #1)
- PSV Script (included with the instructions for Form #1)

The number of forms and pieces of equipment are determined by local staffing configurations and the anticipated participant flow. If available, a spare sphygmomanometer should be on-hand as backup.

If SV1 is to be held in conjunction with the PSV, additional forms and equipment are also needed (see Chapter 07 for details).

Conducting the Prescreening Visit

The procedures for conducting the PSV vary depending on whether it is being done over the phone or in person. This section provides procedures to cover each of these situations.

In general, however, the following sequence of activities will occur:

- Greet the participant
- Describe the study and answer the participant's questions
- Administer informed consent form (if appropriate)
- Administer the Prescreen Eligibility Form
- If face-to-face, conduct a single, non-RZ blood pressure measurement (optional)
- Schedule or conduct SV1 if eligible

Procedures for Conducting the Visit by Phone

At most sites, the initial direct contact between participants and clinic staff will most often be by telephone. Potential participants will usually be responding either to a direct mailing, radio advertisement, or some other recruitment effort. The level of knowledge about the study will vary greatly among respondents depending on the manner in which the participant heard about the study. For example, if the participant has received a copy of the PREMIER brochure, she may already be aware of some of the study's requirements and is likely to satisfy many of the PSV eligibility requirements.

Greet the Participant

Telephone staff should identify themselves by name and should indicate the name of the institution where they work. For example,

> "Hello, <u>name of institution</u>, this is <u>first name of staffer</u> speaking. May I help you?"

The participant will then identify herself and ask to speak with someone about the study. Participants may either identify the study by name or they may refer to it as the "blood pressure study" or use other similar language. Be sure that whoever answers the phones, if the line is used for more than one study, is familiar enough with the study and the recruitment materials to be able to properly refer the participant to a PREMIER staff member.

Describe the Study and Administer Prescreen Eligibility Form

The PREMIER staff member should quickly confirm that the participant is calling about participating in the study, provide a brief overview, and begin to administer the Prescreen Eligibility Form. For example,

"That's right, the name of the study is PREMIER. Let me tell you a little bit about the study, and then, if you are still interested, I have a few quick questions to ask you to see if you might be eligible to participate."

[Use script to review the key points of the study with the participant. A sample script is included in the instructions for Form #1]

"Does the study sound like something you might be interested in?"

If No,

"Well, thanks for your interest anyway."

[Enter "No" for the outcome of question #23 on Form #1,
and code the visit outcome as "ineligible". Or do not fill out a Form #1 at all]

If Yes,

"Great. What I'd like to do then is to ask you a few questions and, if you are still eligible, schedule you for a clinic visit. Are you ready?"

[Enter "Yes" for the outcome of question #23 on Form #1]

Begin administering the Prescreen Eligibility Form, the instructions for which may be found in the Forms Manual. At any point that it becomes evident that the participant is not eligible, you can terminate the contact.

Procedures for Conducting the Visit in Person

In some cases, such as health fairs, the initial contact with the participant will be in person. Depending on the nature of these contacts, the participants may or may not have heard about the study when they meet the study staff person. For example, they may simply think they are waiting for a free blood pressure screening, or they may have been given a copy of the PREMIER brochure to read while they were waiting in line. If blood pressure is measured as the first part of the visit and the participant is ineligible (see guidelines below), the Prescreen Eligibility Form need not be completed.

Describe the Study and Administer Prescreen Eligibility Form

Whenever it makes sense to do so in the context of the screening, the PREMIER staff member should introduce herself as part of the study, provide a brief overview of the study, and begin to administer the Prescreen Eligibility Form. For example,

"Your blood pressure is xxx over xxx, which is above the optimal range, and as a result you might be eligible to participate in a study we are doing to help people reduce their

blood pressure without medications. The name of the study is PREMIER. Let me tell you a little bit about the study, and then, if you are still interested, I have a few quick questions to ask you to see if you might still be eligible to participate."

[Use script to review the key points of the study with the participant. A sample script is included in the instructions for Form #1]

"Does the study sound like something you might be interested in?"

If No,

"Well, thanks for your interest anyway."

[Enter "No" for the outcome of question #23 on Form #1,
and code the visit outcome as "ineligible". Or do not fill out a Form #1 at all]

If Yes,

"Great. What I'd like to do then is to ask you a few questions and, if you are still eligible, schedule you for a clinic visit. Are you ready?"

[Enter "Yes" for the outcome of question #23 on Form #1]

Begin administering the Prescreen Eligibility Form, the instructions for which may be found in the Forms Manual. At any point that it becomes evident that the participant is not eligible, you can terminate the visit.

Assess Blood Pressure (Optional)

The optional PSV blood pressure assessment consists of a single, non-RZ blood pressure measurement conducted in a seated position. No eligibility limits are established for the PSV blood pressure measurement, although for safety reasons participants with a SBP $\geq$ 180 mm Hg or a DBP $\geq$ 110 mm Hg must be referred to their provider within one week and excluded from further participation. It is recommended that individuals with a SBP less than 118 mm Hg or a DBP less than 78 also be excluded. Individual clinical centers may choose to use more restrictive upper limits.

Ending the Prescreening Visit

If, after completing the Prescreen Eligibility Form (Form #1) and blood pressure assessment, the participant is ineligible, thank her for her time and interest and indicate that she is not eligible to participate in the study. Clinical centers are encouraged to tell participants the reason for exclusion.

If the participant is eligible to continue in the study, schedule a date for the SV1 visit and thank the participant for his interest in the study.

After the Prescreening Visit

The Prescreen Eligibility Form (Form #1) is entered into the data entry/management system only for participants who are eligible to continue onto SV1. Clinical centers who wish to track information for ineligible participants will need to create their own database for this purpose.

If the participant is eligible, make sure that the following items have been completed:

- The participant's contact information on the first page of the Prescreen Eligibility Form. At least the name and phone number should be completed at this time. Sites can choose to complete the rest of the contact information at a later date.
- The screening questions on page 2. These are not entered but they must be completed for eligible participants.
- All questions on page 3. These items will be entered.

When the Prescreen Eligibility Form (Form #1) is entered, the data entry application assigns a unique, anonymous study ID#. Record this ID# on the Prescreen Eligibility Form. After entry of the Prescreen Eligibility Form, the data entry person or the clinic coordinator can print out participant labels from the data management application to use on future forms.

Once labels have been printed, attach one to each of the three pages of the Prescreen Eligibility Form. At this point the first page of the form, which contains contact information, should be removed from the rest of the form and filed separately so that identifying information is not inadvertently faxed or mailed to the Coordinating Center. The final two pages of the form should

then identify the participant only through his anonymous study ID and can therefore be safely faxed or mailed.

Participant IDs are assigned using the following algorithm: The first three letters of the participant's last name, followed by the first two letters of the first name, followed by a one-digit site ID number, followed by a four-digit number that is unique to that site. This latter number is assigned sequentially at each site, starting with 0001. If the last name or first name has fewer characters than needed to use this algorithm, an "X" will be used as a placeholder. For example, if the participant's name is Sue Wu, the first five characters of the ID will be WUXSU. When entering data or looking up data in the data entry/management application, the clinic coordinator will need to include the "X" in the participant's ID. (See Data Entry and Data Management User's Manuals for further information on ID numbers.)

Summary of Edits

7. Screening Visit 1 (SV1)

Overview

Screening visit 1 is the first of three formal screening visits to determine eligibility for PREMIER. It is intended to be a relatively brief visit that identifies major medical exclusions via the use of blood pressure measurements and questionnaire data. More invasive and time consuming procedures, including the collection of most baseline data, is deferred to the subsequent screening visits.

The SV1 may occur at any time within 4 months of the PSV, including the day of the PSV. If the SV1 is scheduled to occur more than 4 months after the PSV, the PSV data are invalid and must be recollected prior to obtaining SV1 data. If a participant is excluded on or after SV1, that individual cannot be rescreened for the same cohort. The participant may, however, be rescreened for later cohorts. Staff should be aware that randomization will occur no more than 6 months after SV1.

At the conclusion of SV1, staff may also choose to give participants materials and instructions for completion of a 24-hour urine collection. In addition, a number of questionnaires may be completed at any time during the screening period. These include the Patient History Questionnaire, and a number of psychosocial questionnaires. In order to minimize burden to both staff and participants, however, it is suggested that these questionnaires not be given to participants until after they complete the SV2 visit and are found eligible to continue to SV3.

Setting

The SV1 visit may take place at the clinical center or at a location in the community convenient to the population being recruited. If conducted offsite, the SV1 will usually be conducted in conjunction with the PSV visit. Persons who are eligible at PSV may immediately receive an SV1 visit or they may be scheduled for an SV1 visit at a later time. In order to conduct the SV1 visit in an off-site location, it is essential that appropriate space and facilities are available. This requires a quiet, private or semi-private setting where the required relaxed waiting time can occur before a random zero blood pressure is taken, and an interviewing setting that permits privacy of responses to the questions that are asked.

If the SV1 visit is conducted at the same time as the PSV visit, the PREMIER staff person should leave the room at the end of the PSV visit and ask the participant to sit quietly for five minutes with his legs uncrossed. The SV1 visit is then conducted.

Preparations for SV1 Visit

The following materials are needed to conduct the SV1.

- Study charts for scheduled participants (if available)
- Random zero sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- Stadiometer
- Scale
- Consent materials (if required by local IRB; see Chapter 5)
- SV1 Visit Form (Form #3)
- SV1 Blood Pressure Form (Form #2)
- Blood Pressure Escape Form – Screening (Form #32)
- Eligibility Questionnaire (Form #4)
- Rose Questionnaire — PVD (Form #5)
- Rose Questionnaire — Angina (Form #6)
- Diet and Physical Activity Change Checklist (Form #8)
- SV1/SV2 Activity Fact Sheet (Form #106)
- SV1 BMI Reference Chart (included with the instructions for Form #3)
- Participant Closeout Form (Form #28)
- Participant Contact Information Sheet (Form #100)

In addition, the following materials should also be on hand in case the PSV needs to be redone.

- Prescreen Eligibility Form (Form #1)

The number of forms and pieces of equipment are determined by local staffing configurations and the anticipated participant flow. If available, a spare sphygmomanometer should be available as backup.

If the Prescreen Eligibility Form has already been entered, the participant will have been issued a study ID and preprinted ID labels should be available to use on the forms. If, however, this information is not available, then place the participant's name on each page of each completed form and keep these forms together with the Prescreen Eligibility Form. Once an ID is assigned and ID labels are available, they should be placed on all completed SV1 forms.

If a participant has been screened before, but no study ID exists and a hard copy of the Prescreen Eligibility Form cannot be found, then it must be readministered before the visit can proceed. In this case any old versions of the Prescreen Eligibility Form, if subsequently found, should be discarded.

Conducting the SV1 Visit

SV1 activities are listed below. If required, obtain consent first. Whether consent is required or not, briefly re-describe PREMIER and obtain the participant's assurance that he is interested in participating. In general, blood pressure should be done before the other procedures because the forms need not be administered if the individual is not blood pressure eligible.

- Confirm participant ID and check visit window
- Obtain consent (if required by local procedures)
- Complete the Participant Contact Information form (Form #100)
- Measure blood pressure (Form #2)
- Complete the Eligibility Questionnaire (Form #4)
- Review study and confirm interest
- Complete the Diet and Physical Activity Change Checklist (Form #8)
- Weigh participant, measure height, and check BMI (Form #3)
- Complete the Rose PVD (Form #5) and Rose Angina Questionnaires (Form #6)
- Record events and final eligibility status on the SV1 Visit Form (Form #3)

Confirm participant ID and check visit window

Before each screening visit, clinical center staff should confirm the participant ID and check the visit window. The SV1 visit must occur within 4 months of the PSV visit. If this is not the case, then the PSV must be repeated. This holds even if the data from the first PSV has been entered into the computer. When the new PSV is entered, the computer will generate a new study ID for the participant. It will also be necessary to use a Participant Closeout Form (#28) to close out the old study ID in the data management system.

Obtain informed consent (if applicable)

If informed consent for the screening visits was not obtained as part of the PSV, then it must be obtained now.

Complete the Participant Contact Information form (Form #100))

Ask the participant to complete the Participant Contact Information Form (Form #100). Review to be sure participant has given permission for contacting their physician. If not, go over this with the participant.

Measure blood pressure (Form #2)

Take the participant's blood pressure using the random zero sphygmomanometer and the procedures described in MOP Chapter 17 (Blood Pressure Assessment). The cuff size must be

appropriate. If it is impossible to get an accurate measurement (e.g., if large cuff covers the antecubital fossa or arm circumference is >52 cm.) the participant is excluded.

If the sum of two systolic blood pressures is between 235 and 340 mm Hg and the sum of the two diastolic blood pressures is between 155 and 200 mm Hg, the participant is eligible to continue to SV2. Participants who are excluded based on blood pressure readings above these limits need to be referred to a physician for further evaluation. The timing of the referral, within one week or within one month, depends on the threshold level that is reached (see Chapter 23, Safety Monitoring). These threshold levels are also shown on the SV1 Blood Pressure Form. If escape levels are reached, the Blood Pressure Escape Form – Screening (Form #32) also needs to be completed, with one copy placed in the participant's chart at the site and one copy sent to the CC.

Eligibility Questionnaire (Form #4)

The Eligibility Questionnaire is primarily designed to identify persons who are ineligible for medical reasons. It also asks about a variety of other eligibility criteria. This form should be completed as part of the SV1 visit. It can be sent to the participant to complete at home prior to the visit, or simply given to the participant to complete during the visit. Inform participants that, when they have questions or are unsure about the answer to an item, they should check "unsure" and write a comment or question in the comment section for that item so that it can be reviewed with a staff person later.

Regardless of when the form is completed, a clinical center staff person should review it with the participant to verify its completeness and to attempt to resolve any "unsure" items. Be sure to place a label with the participant's study ID on each page of the form. If an ID has not yet been assigned, write the participant's name on each page of the form and keep the form together with the Prescreen Eligibility Form.

Although the Eligibility Questionnaire asks participants about their use of certain exclusionary medications, it is not intended as a complete assessment of medication use. This occurs during SV2. Instruct participants to bring to the SV2 visit all medications and over-the-counter products (including vitamins, supplements, and other non-prescription drugs) that they regularly take.

Review the study (Form #106) and confirm participant interest

Briefly describe PREMIER again, emphasizing the commitment required of participants. Give participant the SV1/SV2 Activity Fact Sheet (Form #106). Stress how important it is that those who enroll in the study follow through and complete the study, and confirm that the participant thinks s/he would like to participate if eligible.

Diet and Physical Activity Change Checklist (Form #8)

The Diet and Physical Activity Change Checklist is an initial attempt to identify people who are unwilling to comply with any of the various components of the PREMIER interventions. This is a self-administered form that can be completed at home prior to the visit or by the participant during the visit. In either case, participants must review the SV1/SV2 Activity Fact Sheet prior to completing the checklist. Review the form with the participant for completeness and, if he has any questions about specific items, discuss them with him. To be eligible to continue, the participant must answer "Yes" or "Maybe" to every item (see coding instructions for Form #8).

Measure participant's weight and height and check BMI (Form #3)

Measure the participant's weight and height per the protocol outlined in MOP Chapter 20, Other Clinical Measurements. Enter the height and weight on the SV1 Visit Form and note the eligibility status. Although heights are measured in centimeters (rounded to the nearest 0.1 cm), weights are measured and recorded in pounds (to the nearest 0.25 pounds). Refer to the SV1 BMI Reference Chart (found in the instructions for Form #3) to determine if the participant is BMI eligible.

Rose PVD and Angina Questionnaires (Forms #5 and #6)

Participants who are still eligible after completing all of the above activities should next complete both the Rose PVD and the Rose Angina questionnaires. These should be the last questionnaires or measurements completed as part of the visit, and should only be given to eligible individuals. This is because a positive response to either questionnaire triggers a mandatory referral to the participant's physician, including helping the participant find one if he does not already have one. Note that, if the participant were to have completed these forms at home prior to the visit, for instance, then the clinical centers would be ethically compelled to review the forms at the visit, even if the participant were already excluded for, say, high blood pressure.

The two Rose questionnaires are intended to be interviewer-administered. However, they can be self-administered if a clinic staff member carefully reviews them with the participant beforehand (to explain the skip patterns). The staff person will also need to go over the forms after they are completed to make sure they were filled out completely and accurately, and to answer any questions the participant may have.

Anyone who is positive on the angina questionnaire must be referred to her personal physician for evaluation and cannot participate unless approved to do so by both her physician and a study clinician. If the participant does not have a personal physician, she must be referred to one. The participant's personal physician will be asked to confirm that the participant has had a negative exercise stress test within the last 6 months (defined as 6 months prior to the date the physician contacts PREMIER with the information), and that the physician approves of the patient

participating in the PREMIER interventions. Next, a study clinician must review the study chart and also agree that the participant may continue in the study. If the decision is made that the participant should not continue, she can be excluded using the Participant Closeout Form (#28). If the participant will be continuing in the study (with personal physician and study clinician approval) this needs to be indicated on the Pre-Randomization Checklist (Form #19). The participant can continue in the screening process while this follow-up is taking place.

Anyone who is positive on the PVD questionnaire must be referred to her personal physician for evaluation and cannot participate unless approved to do so by both her physician and a study clinician. If the decision is made that the participant should not continue, she can be excluded using the Participant Closeout Form (#28). If the participant will be continuing in the study (with personal physician and study clinician approval) this needs to be indicated on the Pre-Randomization Checklist (Form #19). The participant can continue in the screening process while this follow-up is taking place.

SV1 Visit Form (Form #3)

After each portion of the visit is completed, a PREMIER staff person should check the appropriate "Done?" box on the SV1 Visit Form and (if applicable) indicate whether the participant is eligible or not eligible to continue based on that portion of the visit. At the end of the visit, a staff person should review this form to make sure that the participant has completed all of the necessary components. This staff person should also make sure that a single outcome status is coded at the bottom of the form and should enter her staff ID# in the "Reviewed by staff ID" field.

If a participant is excluded at the investigator's discretion (i.e., not as part of the regular screening activities for that visit), complete the Participant Closeout Form (Form #28) to record the reason for the exclusion. The SV1 Visit Form does not need to be entered in this situation.

Ending SV1

To complete the SV1 visit, do the following:

If the participant is ineligible

You may inform participants of their eligibility status and terminate the visit whenever it is clear that they are not eligible for PREMIER. Explain the reasons for ineligibility to the participant. Enter the visit outcome status onto the SV1 Visit Form.

If the participant is eligible

If participant is eligible, schedule an appointment for SV2 at least seven days from SV1. The clinical center may wish to give participants some of the non-eligibility questionnaires (e.g., the

psychosocial questionnaires or the patient history questionnaire) at this time to complete at home and return at the SV2 visit. This is discouraged, however, since many of these participants will go on to become ineligible at SV2. Instead, clinic staff are encouraged to distribute these forms after completion of the SV2 visit.

Finally, clinic staff need to enter the various forms into the data entry system. This should be done within two weeks of the visit, and preferably within one week. The SV1 Visit Form (Form #3) should not be entered until all of the other forms related to the visit have been entered.

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Use Form #201, Weight Loss Medications that Affect Blood Pressure, when completing Form #11, Baseline Medication Use Questionnaire

8. Screening Visit 2 (SV2)

Overview

The purpose of SV2 is to continue to screen participants for eligibility as accurately and efficiently as possible. This visit occurs at least 7 days after SV1. The activities listed below include completion of the Medication Use Questionnaire; measurement of blood pressure; collection of a non-fasting blood sample for creatinine and glucose; distribution of the instructions and supplies for the 24-hour urine collection; and distribution of instructions and form for the one-day Food Record.

The Food Record is to be completed by the participant and returned at SV3. The SV2 Blood Pressure eligibility is determined by summing up four total BPs, the two BPs from SV1 and the two BPs from SV2. Participants who are found eligible at the end of this visit are scheduled for an SV3 visit.

The visit may also be used to perform the fasting blood draw and to receive and process the 24-hour urine specimen, both of which must occur at some time between SV1 and randomization. The blood draw, which requires a minimum of a 12-hour fast, is processed centrally for analysis of lipids, insulin, glucose, and homocysteine. The 24-hour urine collection is analyzed centrally for sodium, potassium, phosphorus, creatinine, and urea nitrogen (See Chapter 21, Central Laboratory Procedures, for details). The instructions for processing the fasting blood and urine collections should be followed no matter when the specimen is returned. The Central Lab Collection Form—Fasting Blood (Form #21) and the Central Lab Collection Form—24-hour Urine (Form #20) are used for processing the blood and urine samples.

A number of questionnaires may also be completed at any time prior to randomization. These include the Patient History Questionnaire and a number of psychosocial questionnaires. It is suggested that they not be given to participants until after they complete the SV2 visit and are found eligible to continue to SV3. Although these forms do not have to be entered prior to randomization, they should be completed prior to the randomization/intervention visit so that ample time is available to resolve data edits. Record the completion of these questionnaires on Form #19.

Setting

The SV2 visit takes place at the clinical center. It requires a quiet, private or semi-private setting where the participant can wait relaxed prior to the random zero blood pressure measurement. Questionnaires also need to be administered and reviewed in a setting that permits privacy for the participant.

Preparations for SV2

The following materials are needed to conduct the SV2.

- Study charts for scheduled participants
- Consent materials (if required by local IRB, see Chapter 4)
- Random zero sphygmomanometer, standard sphygmomanometer and stethoscope
- SV2 Blood Pressure Form (Form #9)
- Baseline Medication Use Questionnaire (Form #11)
- Weight Loss Medications that Affect Blood Pressure (Form #201)
- Local Lab Worksheet (Form #12)
- Local laboratory chemistry panel blood supplies
- Participant instructions and materials for 24-hour urine
- SV2 Visit Form (Form #10)
- One-Day Food Record Screening Form (Form #200) and instructions
- SV1/SV2 Activity Fact Sheet (Form #106)
- Blood Pressure Escape Form – Screening (Form #32)
- Participant Closeout Form (Form #28)

Preprinted ID labels should be available to use on the forms. The number of forms and pieces of equipment are determined by local staffing configurations and the anticipated participant flow. If available, a spare (back up) sphygmomanometer should be available.

Conducting SV2

SV2 activities are listed below. If required, obtain consent first. Whether consent is required or not, briefly re-describe PREMIER and obtain the participant's assurance that he is interested in participating.

In general, blood pressure should be measured before doing other procedures because the forms need not be administered if the individual is not blood pressure eligible. Performing the SV2 activities in the order listed below should provide the most efficient identification of ineligible subjects. SV2 may be politely concluded at any point after an exclusionary condition or situation has been identified.

- Attach a pre-printed participant label on all forms
- Confirm participant ID and check visit window
- Obtain informed consent (if required)
- Review study and confirm interest (Form #106)
- Measure blood pressure (Form #9)
- Complete Medication Use Questionnaire (Form #11)
- Collect non-fasting blood specimen (for local lab)

- Optional: distribute instructions and supplies for the 24-hour urine sample (Note: women must complete collection when NOT menstruating)
- Distribute Food Record Form (Form #200) and instructions
- Record events and eligibility status on the SV2 Visit Form (Form #10)

Confirm ID, check visit window, and obtain informed consent

Confirm the participant ID and check the visit window. SV2 must occur at least seven days after SV1. If necessary, obtain informed consent for the visit.

Review the Study (Form #106) and confirm participant interest

Briefly describe PREMIER again, emphasizing the commitment required of participants. Give participants the SV1/SV2 Activity Fact Sheet (Form #106). Stress how important it is that those who enroll in the study follow through and complete the study, and confirm that participant thinks she would like to participate if eligible.

Measure blood pressure (Form #9)

Take the participant's blood pressure using the random zero sphygmomanometer and the procedures described in MOP Chapter 17 (Blood Pressure Assessment). **Be sure to use the same cuff size as was used in SV1, except as noted in chapter 17.** If the participant cuff size is found to differ from that used during SV1 and the cuff size is not appropriate for the participant, a replacement blood pressure should be taken using the proper cuff if participant has not left the clinic. Otherwise the original measurement stands.

If the cumulative sum of the four systolic blood pressure measurements from SV1 and SV2 is between 474 and 661 mm Hg and the cumulative sum of the four SV1 and SV2 diastolic blood pressure measurements is between 314 and 393 mm Hg (inclusive), the participant is eligible to continue to SV3.

Participants who are excluded based on blood pressure readings above these limits need to be referred to a physician for further evaluation. The timing of the referral, within one week or within one month, depends on the threshold level that is reached (see Chapter 23, Safety Monitoring). These threshold levels are also shown on the SV2 Blood Pressure Form. If the threshold levels are exceeded, the Blood Pressure Escape Form – Screening (Form #32) needs to be completed, with one copy placed in the participant's study chart and one copy sent to the CC. The participant may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment even if the BP is lower than the above limits.

If the cuff size is found to be different from that used during SV1 (except as noted in chapter 17), and the participant has not left the building, a replacement blood pressure should be taken using the appropriate size cuff. Otherwise, the original measurement will stand.

Complete the Baseline Medication Use Questionnaire (Form #11)

Confirm that the participant has brought in all medications, over-the-counter products, or nutritional supplements that they are currently using. Check the participant's medication containers and complete the Baseline Medication Use Questionnaire. If the participant fails to bring her current medications, it will be necessary to call the participant at home to review her medications. Use Form #201, Weight Loss Medications that Affect Blood Pressure, to check weight loss medications.

If the participant is eligible to continue and reports taking ***any*** medications, a PREMIER clinician must review and sign the form assuring that the participant is not using any exclusionary products. If the participant is taking a medication that is clearly exclusionary, the form does not need to be reviewed by a clinician.

Collect laboratory samples

Draw the necessary non-fasting blood samples for the local exclusionary labs. Follow the procedures outlined in MOP Chapter 21 for collection and processing. Remind the participant that you may recall him for additional blood draws if any questions arise. The Local Lab Worksheet (Form #12) is used to track: whether the blood specimens are collected; the creatinine and glucose results; if a repeat test is ordered; and the eligibility status of the participant based on the results of the test.

Lab tests can be repeated at investigator discretion. Each test can only be repeated once. Clinical centers can choose to do fasting or non-fasting blood collections for the initial or repeat tests. Eligibility is based on the results of the repeat specimen, if one is done.

The Local Lab Worksheet cannot be completed until after results from the local lab are received. So, the SV2 Visit Form cannot be completed until the results are in.

Distribute urine container and instructions for the 24-hour urine sample

Distribute the 24-hour urine container and instructions to the participant. Review the instructions. Remind the participant that the sample needs to be returned to the clinic within 24 hours of collection. In unusual circumstances, such as when collection starts on a Friday, samples may be kept refrigerated and returned to the clinic within 48 hours. The 24-hour urine sample must be returned before the randomization visit, preferably at SV3. Some clinical centers may prefer to wait to initiate this process until after participants are SV3 eligible. If this is the case, make a note of this on the SV2 Visit Form, and also add a reminder note to the SV3 Visit Form (#15) that participant will need to get their 24-hour urine materials at that visit.

Make sure that a label is affixed to the collection jug. Refer to the Interim Visit Chapter (Chapter 10) of the MOP for detailed instructions. Note: Instruct pre-menopausal women to collect the 24-hour urine specimen when they are not menstruating.

Distribute instructions and form for the One-Day Food Record Screening Form (Form #200)

Distribute the One-Day Food Record Screening Form to the participant, and review the instructions for filling it out. Inform the participant that the form needs to be completed and returned at the SV3 visit. Make sure that the participant's label is on each page of the form. Explain to participant that completing this form is a requirement of the study.

SV2 Visit Form (Form #10)

After each portion of the visit is completed, a PREMIER staff person should check the appropriate "Done?" box on the SV2 Visit Form and (if applicable) indicate whether the participant is eligible or not eligible to continue based on information gathered at the visit. At the end of the visit a staff person should review this form to make sure that the participant has completed all of the necessary components. This person should also make sure that a single eligibility outcome status is coded at the bottom of the form and should enter his ID in the appropriate field. Eligibility status on the SV2 Visit Form cannot be indicated until after the medication review and after a clinician signs the form.

If a participant is excluded at the investigator's discretion (i.e., not as part of the regular screening activities for this visit), complete the Participant Closeout Form (Form #28) to record the reason for the exclusion. In this case, do not enter an outcome on the SV2 Visit Form, and do not enter the SV2 Visit Form.

Ending SV2

To complete the SV2 visit, do the following:

If the participant is ineligible:

You may inform the participant of her eligibility status and terminate the visit wherever it is clear that the individual is not eligible for PREMIER. Explain the reasons for ineligibility to the participant. Enter the visit outcome status on the SV2 Visit Form.

If the participant is eligible:

Schedule an appointment for SV3 at least 7 days after SV2. The Clinical Center may wish to give participants some of the non-eligibility questionnaires at this time to complete at home and return at the SV3 visit. Warn the participant that it is possible that their lab test results may make

them ineligible. Clinical centers may decide to put off scheduling the SV3 Visit until after the local lab test results have been received and the participant is determined to be eligible.

When all data on the SV2 Visit Form have been collected, enter the SV2 BP Form, the Medication Use Questionnaire, and the Local Lab Worksheet into the data entry/management system. After those forms have been entered, enter the SV2 Visit Form. All of this data entry should be completed within two weeks of the visit; preferably within one week.

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Corrected reference to fasting blood to state that a 12 hour fast is required.

Summary of changes between Version 1.1 and 1.2:

- Titles of Forms #104 and #105 changed to "Food Interview" from "Diet Recall"
- Added note that for Cohort 1, PAR will be administered at the interim visit rather than at SV3

Summary of changes between Version 1.2 and 1.3:

- For cohorts 2-4, additional baseline blood samples are drawn to be analysed at CDC for folate, carotenoids, and Vitamin B-12
- Title of Form #16 changed to "Baseline Symptoms Questionnaire"
- PAR may be collected either at SV3 or during the interim period

9. Screening Visit 3 (SV3)

Overview

Screening Visit 3, which must occur at least 7 days after SV2, is the third visit at which participants are screened to determine eligibility for PREMIER. Activities include BP measurement, completion of the 7-Day Physical Activity Recall and Symptoms Questionnaire, a review of the Food Record and the SV3 Activity Fact Sheet, and a motivational session with a staff interventionist.

The SV3 Blood Pressure eligibility is determined by summing up six total BPs, the two BPs from SV1, the two BPs from SV2, and the two BPs from SV3. Participants who are found to be eligible for the trial at the end of SV3 are provided with instructions to prepare them to complete the 24-hour food interviews to be administered by telephone by the Pennsylvania State University Diet Assessment Center.

Other measurements

The visit may also be used to perform the fasting blood draw and to receive and process the 24-hour urine specimen, both of which must occur at some time between SV1 and randomization. The blood draw, which requires an 12-hour fast, is processed centrally for analysis of lipids, insulin, glucose, and homocysteine. For cohorts 2 – 4, blood is also drawn to be analysed at CDC for folate, carotenoids, and vitamin B-12. The 24-hour urine collection is analyzed centrally for sodium, potassium, phosphorus, creatinine, and urea nitrogen (See Chapter 21, Central Laboratory Procedures, for details). The instructions for processing the fasting blood and urine collections should be followed no matter when the specimen is returned. The Central Lab Collection Form—Fasting Blood (Form #21) and the Central Lab Collection Form—24-hour Urine (Form #20) are used for processing the blood and urine samples.

A number of questionnaires may also be completed at any time during the screening period. These include the Patient History Questionnaire and a number of psychosocial questionnaires. These can be completed at any time prior to randomization. However it is suggested that they not be given to participants until after they complete the SV2 visit and are found eligible to continue to SV3. Although these forms do not have to be entered prior to randomization, it is strongly recommended that the entry be done prior to the randomization/intervention visit so that ample time is available to resolve data edits. Record the completion of these questionnaires on Form #19.

The Eligibility Review Questionnaire (Form #17, which must be done within 30 days of randomization) may be done at this visit.

Setting

The SV3 visit takes place at the clinical center. It requires a quiet, private setting where participants can wait prior to the blood pressure measurement. Questionnaires also need to be administered and reviewed in a setting that permits privacy for the participant.

Preparations for SV3

The exact number of forms and pieces of equipment needed for the SV3 visit is determined by local staffing configurations and the anticipated participant flow. If available, a spare sphygmomanometer should be available as backup. At a minimum, the following materials are needed to conduct the SV3.

- Study charts for scheduled participants
- Consent materials (if required by local IRB. See Chapter 4, Human Subjects)
- Random zero sphygmomanometer, standard sphygmomanometer and stethoscope
- SV3 Visit Form (Form #15)
- SV3 Blood Pressure Form (Form #14)
- Baseline Symptoms Questionnaire (Form #16)
- 7-Day Physical Activity Recall (Form #18)
- SV3 Activity Fact Sheet (Form #107)
- Screening Motivational Session Notes (Form #41)
- Diet and Physical Activity Change Questionnaire (Form #40)
- Food Interview Instruction Sheet (Form #104)
- Food Interview Informational Poster
- Food Interview Convenient Time Schedule (Form #105)
- Food Record and Instructions (Form #200) [if needs to be repeated]
- Eligibility Review Questionnaire (Form #17) [if Eligibility Questionnaire is not within 30 days of randomization, and SV3 visit is within 30 days of randomization)

Conducting SV3

In general, performing the SV3 activities in the order listed below should provide the most efficient identification of ineligible subjects. The visit may be politely concluded at any point after an exclusionary condition or situation has been identified.

- Confirm participant ID, check visit window, and obtain informed consent
- Take participant's random zero blood pressure readings and note eligibility on SV3 Visit Form
- Administer Baseline Symptoms Questionnaire
- Review Food Record or give new one if Food Record needs to be repeated
- Assess willingness to participate

- Review SV3 Activity Fact Sheet
- Conduct screening motivational session
- Administer Diet and Physical Activity Change Questionnaire
- Administer 7-Day Physical Activity Questionnaire
- Review Food Interview instructions, complete Convenient Time Schedule, and fax Food Interview Convenient Time Schedule to Pennsylvania State University Diet Assessment Center

Confirm ID, Check Visit Window, and Obtain Informed Consent

Generate pre-printed labels from the data management system and place the labels on all appropriate SV3 forms. Confirm that at least seven days have elapsed since the SV2 visit.

If necessary, obtain informed consent for the visit.

Measure Blood Pressure

Take the participant's blood pressure using the random zero device and the procedures described in Chapter 17 (Blood Pressure Assessment). **Be sure to use the same cuff size as was used at SV1, except as noted in Chapter 17, (Blood Pressure Assessment).** If the participant cuff size is found to differ from that used during SV1 (except as noted in Chapter 17) and the cuff size is not appropriate for the participant, a replacement blood pressure should be taken using the proper cuff if participant has not left the clinic. Otherwise the original measurement stands. Record the measurements on the SV3 Blood Pressure Form (Form #14). If the cumulative sum of the SV1, SV2, and SV3 systolic blood pressure measurements is between 717 and 956 and the cumulative sum of the SV1, SV2, and SV3 diastolic blood pressure measurements is between 477 and 572 mm Hg, the participant is blood pressure-eligible for randomization.

Participants who are excluded based on blood pressure readings outside these limits need to be referred to a physician for further evaluation. The timing of the referral, within one week or within one month, depends on the threshold level that is reached (see Chapter 23, Safety Monitoring). These threshold levels are also shown on the SV3 Blood Pressure Form. If the thresholds are exceeded, the Blood Pressure Escape Form – Screening (Form #32) also needs to be completed, with one copy placed in the participant's study chart and one copy sent to the CC. The participant may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment even if the BP is lower than the above limits.

Administer the Baseline Symptoms Questionnaire

Ask the participant to complete the Baseline Symptoms Questionnaire (Form #16). A study clinician must sign the form. Check the appropriate box on the SV3 Visit Form to indicate the Baseline Symptoms Questionnaire has been completed.

Review the One-Day Food Record Screening Form

The One-Day Food Record Screening Form (#200) can be reviewed by any staff member. Make sure the Food Record is returned and completed by the participant. The Food Record is considered acceptable if the participant lists at least 4 food items with an attempt to indicate amounts for each food item. If these minimum requirements are not met, the participant is asked to repeat the food record. Indicate on the SV3 Visit Form whether the food record was complete, or whether it needed to be repeated.

Assess the Participant's Willingness to Participate in the Study

The next three forms in this section must be administered by an interventionist. Go over with the participant the SV3 Activity Fact Sheet (Form #107) to once again review the requirements of the study and conduct the Screening Motivation Session (Form #41) to explore the participant's interest and potential ambivalence. Administer the Diet and Physical Activity Change Questionnaire (Form #40) to ask whether the participant is willing and able to participate in the study activities and procedures. If the participant answers yes to the global question on Form #40, he is eligible to continue. Check the appropriate boxes on the SV3 Visit Form to indicate the SV3 Activity Fact Sheet was reviewed, the motivational session was delivered, and the eligibility status regarding the Diet and Physical Activity Change Questionnaire.

Administer 7-Day Physical Activity Recall

This must be administered by staff certified in PAR technique. Because of the potential for this interview to unblind the interviewer to the participant's treatment status during follow up, staff need to be carefully selected for PAR training. The ideal solution is to use a blinded person who is not taking BP measurements. The other option is an unblinded person, as long as they are not involved in delivering the intervention and do not take BP measurements. Sites can each find their best possible solution given staffing limitations.

See Chapter 22, Physical Activity Assessment, for more details on administering the recall. Complete the 7-Day Physical Activity Recall (Form #18). Check the appropriate box on the SV3 Visit Form indicating the recall was completed.

The PAR may be completed either at SV3 or during the interim period.

Give Instructions for the 24-Hour Food Interview

Give and review with the participant the instructions for the 24-hour food interview (Form #104). Have the participant complete the Food Interview Convenient Time Schedule (Form #105). This form has three pages, one for each time zone. Make sure to use the page with the appropriate time zone. Fax this form to the Pennsylvania State University Diet Assessment Center. Check the appropriate boxes on the SV3 Visit Form indicating the instructions were

given, the schedule was completed, and was faxed to Pennsylvania State University Diet Assessment Center. See Chapter 19 for more details on the 24-hour food interview.

Ending SV3

To complete the SV3 visit, do the following:

- Review the SV3 Visit Form and all other visit forms to make sure the visit is complete.
- Inform the participant of their eligibility status. You may terminate the visit at any point that it is clear that the individual is not eligible for PREMIER. Explain the reasons for ineligibility to the participant.
- If the participant is eligible thus far, remind participant that final eligibility will depend on the completion of the fitness test, fasting blood draw, 24-hour urine collection, pending questionnaires, and two 24-hour food interviews (and food record if not yet completed).
- If the participant was excluded due to escape-level blood pressure criteria, refer him to his physician and complete the BP Escape Form —Screening (Form #32).
- Enter the visit outcome status on the SV3 Visit Form (Form #15).
- Enter all questionnaires and the SV3 BP Form (Form #14) into the data entry application. After those forms have been entered, enter the SV3 Visit Form. All of this data entry should be completed within two weeks of the visit; preferably within one week.

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- p.4, added creatinine to 24-hr urine measurements

Summary of changes between Version 1.1 and 1.2:

- Titles of Forms #104, #105, and informational poster changed to "Food Interview" from "Diet Recall"
- Baseline waist circumference may be measured in the interim period *or* at the R/I visit (protocol change)
- Added note that for Cohort 1, PAR will be administered at the interim visit rather than at SV3

Summary of changes between Version 1.2 and 1.3:

- Added note to blood and urine sample collection instructions referring to Chapter 21 for details on sample handling, processing, acceptability, and requirements for repeat samples.

Summary of changes between Version 1.3 and 1.4:

- For cohorts 2-4, additional baseline blood samples are drawn to be analyzed at CDC for folate, carotenoids, and Vitamin B-12
- PAR may be collected either at SV3 or during the interim period

10. Interim Period Measures

Overview

Participants must complete a fitness assessment and two 24-hour food interviews between Screening Visit 3 and the Randomization/Intervention visit (R/I). Clinical centers should allow at least 3-4 weeks between SV3 and the R/I visit in order to complete these activities.

The interval between SV3 and the R/I visit also should be used to complete, if needed: follow-up of individuals who have a positive Rose Angina or PVD questionnaire; the 24-hour urine collection; the fasting blood draw; the Eligibility Review Questionnaire; the case conference; the fourth baseline blood pressure; and a number of noneligibility questions (see below) whose times of administration are flexible. The randomization consent may also be obtained during this interval.

The timing and order of all of these activities is flexible. However, with the exception of the fourth baseline blood pressure measurement and the randomization consent, clinical centers are strongly encouraged to complete all of the above activities, and enter the relevant data, prior to the R/I visit. This will enable data problems to be detected and resolved prior to randomization. Waiting to complete these activities until the R/I visit may cause delays in randomization, since several of the above forms/activities must be entered, and data edits resolved, before a randomization assignment can be issued.

Required Materials

The following materials are needed to complete the activities described above:

- Pre-Randomization Checklist (Form #19)

<u>Food interview materials</u>

- Food Interview Instruction Sheet (Form #104)
- Food Interview Informational Poster
- Food Interview Convenient Times Schedule (Form #105)

<u>Non-eligibility baseline questionnaires</u>

- Patient History Questionnaire (Form #24)
- Quality of Life Questionnaire (Form #23)
- Perceived Stress Questionnaire (Form #25)
- Exercise Confidence Questionnaire (Form #45)
- Eating Habits Confidence Questionnaire (Form #46)

- Social Support and Eating Habits Questionnaire (Form #47)
- Social Support and Exercise Questionnaire (Form #48)
- Perceived Body Image Questionnaire (Form #49)

Treadmill Fitness Test
(Detailed information on conducting the fitness test is included in Chapter 18).

- Treadmill equipment and materials as specified in Chapter 18.
- Fitness Test Form (Form #26)

Central Lab Specimens Collection
(Detailed information on processing lab samples is included in Chapter 21).

- Fasting blood sample kit (analyzed centrally for total cholesterol, LDL-C, HDL-C, VLDL-C, triglycerides, insulin, glucose, and homocysteine)
- CDC kit for folate, carotenoids, and vitamin B12
- 24-hr urine processing materials (analyzed centrally for Na, K, phosphorus, creatinine, and nitrogen)
- Central Lab Collection Form – Baseline 24hr Urine (Form #20)
- Central Lab Collection Form – Baseline Fasting Blood (Form#21)
- CDC Lab Collection Form – Folate/Carotenoids/Vitamin B12 (Form #77)

Eligibility review

- Eligibility Review Questionnaire (Form #17)

Blood pressure assessment

- Random zero sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- Fourth Baseline Blood Pressure Form (Form #27)
- Blood Pressure Escape Form – Screening (Form #32)

Other

- Randomization Checklist (Form #60)
- Participant Closeout Form (Form #28)
- PAR (Form #18)

Conducting the Interim Data Collection Visit(s)

As noted previously, not all of the following activities may need to be completed between SV3 and the R/I visit. Some may either already have been done, or else may be done at the R/I visit. Except as noted, clinical centers are discouraged from using the latter (R/I) option. In addition, those activities that are done during this interval need not all be done as part of the same visit.

- Confirm participant ID
- Complete the Eligibility Review Questionnaire (if needed)
- Complete/review followup for positive Rose questionnaires (PVD and Angina, if needed)
- Complete/review the non-eligibility baseline questionnaires
- Completion of two 24-hour food interviews
- Collect and process the fasting blood sample
- Collect and process the 24-hour urine specimen
- Conduct the treadmill fitness test and record the results
- Conduct a case conference and determine whether the participant will continue in the study
- Measure 4th Baseline Blood Pressure
- Obtain randomization consent
- Record events and final interim eligibility status on the Pre-Randomization Checklist

Confirm participant ID

Make sure that the participant's ID is on the Pre-Randomization Checklist (Form #19) and any other forms to be completed during the interim period. Clinical center staff should confirm the accuracy of all IDs. Use of preprinted ID labels is recommended.

Complete the Eligibility Review Questionnaire

The Eligibility Questionnaire (Form #4) is asked as part of the SV1 visit and is primarily designed to identify persons who are ineligible for medical reasons. It also asks about a variety of other eligibility criteria. If more than 30 days will have elapsed between the date of the Eligibility Questionnaire (Form #4) and the scheduled R/I visit, complete the Eligibility Review Questionnaire (Form #17) to ensure that no major eligibility criteria have changed. This form, if needed, can be administered at any time within 30 days of the R/I visit. To determine which participants need to have the Eligibility Review Questionnaire administered, run the Ready for Randomization Report (MANAGE08). Some sites may find it easier to complete Form #17 for all participants to avoid computing the 30-day window.

This questionnaire can be sent to the participant to complete at home prior to the visit, or simply given to the participant to complete during the visit. Inform participants that, when they have questions or are unsure about the answer to an item, they should leave it blank and write a comment or question in the comment section for that item so that it can be reviewed with a staff

person later. Regardless of when the form is completed, a clinical center staff person should review it with the participant to verify its completeness and to attempt to resolve any items with comments. Be sure to place a label with the participant's study ID on each page of the form. Any positive response to an eligibility question (see form for explanation of which questions determine eligibility) makes the participant ineligible for randomization. Questions must be resolved, with a clinician if necessary, before a participant can be randomized. For this reason the form should ideally be administered prior to the R/I visit.

The questionnaire must be completed **and entered** prior to randomization.

Complete/review follow-up for positive Rose Questionnaires

If either of the Rose Questionnaires administered at SV1 had a positive outcome, the follow-up with the participant's physician and the study clinician must be completed and noted on the Pre-Randomization Checklist (Form #19) before randomization can occur. Use the worksheets attached to each Rose Questionnaire to document the follow-up process.

Complete/review the non-eligibility baseline questionnaires

A number of questionnaires may optionally occur during the interim period. These include a variety of baseline measures such as the Patient History Questionnaire and various psychosocial questionnaires.

These can be completed at any time prior to randomization, and do not have to be entered prior to randomization. However it is recommended that they be completed prior to the randomization visit so that ample time is available to resolve data edits. Record the completion of these questionnaires on Form #19.

Administer 7-Day Physical Activity Recall

The 7-Day Physical Activity Recall (Form #18) may be completed during the interim period or at SV3. See Chapter 9, SV3, and Chapter 22, Physical Activity Assessment, for more details on administering the recall.

Completion of two 24-hour food interviews

Two unannounced 24-hour food interviews occur during the interim period to establish baseline diet status. These recalls, conducted by telephone by the Diet Assessment Center of Pennsylvania State University, must take place within a 3-week period on nonconsecutive days. Completion of the 2 recalls is a requirement for randomization. The procedure for administration of the interviews is presented in Chapter 19. Penn State will notify the clinical centers once the two interviews have been completed so that this information can be noted in the data management system using Form #19.

Collect and process the 12-hour fasting blood sample and the 24-hour urine specimen

Central lab specimens may be collected at any time between SV3 and randomization if they have not already been obtained. Participants need to be made aware that they cannot be randomized until this specimen has been obtained. It is recommended that they be done at least a few days prior to the randomization visit in case the collection is not successful and needs to be repeated. (See Chapter 21, Central Lab Procedures, regarding requirements for acceptability and repeat samples. Details on handling of samples and processing are also covered in Chapter 21.)

The central lab forms (Forms #20 and #21) and the CDC Lab Collection Form (#77) must be completed prior to randomization, but do not have to be entered prior to randomization. However the relevant boxes on Form #19 must be checked to indicate that acceptable samples were collected.

Conduct the treadmill fitness test and record the results

Baseline cardiorespiratory fitness is determined by submaximal treadmill stress testing. This procedure is described in Chapter 18. Participants must complete the fitness test between SV3 and the R/I visit. Note the completed test on Form #19.

Conduct a case conference

Before scheduling a Randomization/Intervention Visit, sites should plan a brief case conference to discuss each participant. This is a chance for clinical staff to voice any safety or compliance issues they may have with particular participants. The PI at each site is responsible for making a final eligibility decision about each participant for whom there are any questions or concerns.

The outcome of the case conference is entered on the Pre-Randomization Checklist. Participants declared to be ineligible during the case conference are automatically closed out when their checklist is entered.

Measure 4th Baseline Blood Pressure

The 4th baseline blood pressure must be measured at least seven days after SV3 and prior to randomization (including at the R/I visit). Record the outcome of the measure on the Randomization Checklist (Form #60), not the Pre-Randomization Checklist, even if it is taken prior to the R/I visit. Be sure to use the same cuff size as that used at SV1, except as noted in Chapter 17. If the participant cuff size is found to differ from that used during SV1 and the cuff size is not appropriate for the participant, a replacement blood pressure should be taken using the proper cuff if participant has not left the clinic. Otherwise the original measurement stands.

If the participant's blood pressure hits an escape level on this measurement, the participant is excluded from further participation. Enter the 4th Baseline Blood Pressure Form (Form #27), a

BP Escape Form—Screening (Form #32), and then complete the Participant Closeout Form (Form #28). In this case, staff do not need to enter the Pre-Randomization Checklist or any other interim forms.

Measure waist circumference

Measure the participant's waist circumference per the protocol outlined in MOP Chapter 20. Note the measurements on the Randomization Checklist (Form #60) in centimeters to the nearest 0.1 cm.

Obtain randomization consent

Consent to participate in the main trial must be obtained sometime between the SV3 visit and prior to randomization. Enter the outcome on the Randomization Checklist (Form #60). Participants who choose to drop out of the study at this point should be closed out immediately using the Participant Closeout Form (Form #28).

Record events and final eligibility status on the Pre-Randomization Checklist

Review the Pre-Randomization Checklist and all other forms to make sure the data collection is complete and each item has been checked off on the checklist.

Ending the Interim Data Collection Visit(s)

Inform the participant of her eligibility status. The visit may be terminated at any point that it is clear that the individual is not eligible for PREMIER. Explain the reasons for ineligibility to the participant. Enter the visit outcome status on the Pre-Randomization Checklist (Form # 19).

Once all items on the checklist are complete, or the participant is found to be ineligible, enter at least the following two items (in this order):

- Eligibility Review Questionnaire (if any)
- Pre-Randomization Checklist

In addition, any of the non-eligibility baseline forms can be entered (in any order) at this time.

11. RANDOMIZATION/INTERVENTION VISIT (R/I) 3

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Baseline waist circumference may be measured in the interim period or at the R/I visit (protocol change)

Summary of changes between Version 1.1 and 1.2:

- Diastolic BP escape criterion for this visit, p. 11-6 corrected from "sum of two > 199mmHg" to "sum of two > 219mmHg."

Summary of changes between Version 1.2 and 1.3:

- Review the participant's current health status to confirm that the participant is still cleared to continue. If health status has changed, assess whether or not it is still suitable to randomize the participant.

11. Randomization/Intervention Visit (R/I)

Overview

At the Randomization/Intervention visit, participants complete final baseline measurements, are randomized, and have their first intervention visit. Details of the latter are covered in the Intervention MOP. This chapter focuses on the clinic portion of the visit, including randomization.

Participant blood pressure, if collected at this visit, is not used to determine eligibility. However participants are still excluded for safety reasons if this blood pressure exceeds escape levels.

The Randomization/Intervention visit must occur no more than 6 months after the SV1 visit.

Setting

The randomization visit takes place at the clinical center and requires a quiet, private or semi-private setting where the required relaxed waiting time can occur before a random zero blood pressure (if needed) is taken, and an interviewing setting that permits privacy of response to the questions that are asked. Separate facilities must be provided to conduct the first intervention session, which also occurs as part of the R/I, in order to ensure that clinic staff remain blinded to intervention assignment.

Preparations for R/I Visit

If possible, complete and enter the Pre-Randomization Checklist (Form #19) prior to the randomization visit.

At least one day prior to the R/I visit, run the "Ready for Randomization" report, make sure all required forms have been entered, and confirm that the participant is eligible. Missing items must be completed (and if necessary entered) before a randomization assignment can be assigned. This chapter assumes that all of the discretionary activities covered in Chapter 10 (Interim Period Measures), with the exception of the 4th blood pressure measurement and the randomization consent, have been completed prior to the R/I visit.

The following materials are needed to conduct the R/I visit:

- Scale
- Tape Measure
- Randomization Checklist (Form #60)

In addition, the following materials may also be required.

Blood pressure assessment
- Random zero sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- Fourth Baseline Blood Pressure Form (Form #27)
- Blood Pressure Escape Form – Screening (Form #32)

Informed consent
- Consent materials for main trial

Miscellaneous
- Study charts for scheduled participants (if available)
- SV3 Activity Fact Sheet (Form #107)

The number of forms and pieces of equipment are determined by local staffing configurations and the anticipated participant flow. A spare sphygmomanometer should be available as backup.

Conducting the R/I Visit

Activities associated with the R/I visit are listed below.

- Confirm participant ID
- Confirm that the Pre-Randomization Checklist has been completed and entered
- Check visit window
- Review study and confirm interest
- Obtain consent for main trial (if not yet obtained)
- Measure fourth baseline blood pressure (if not yet obtained)
- Measure waist circumference (if not yet obtained)
- Weigh participant
- Record events and final eligibility status on the Randomization Checklist
- Randomize participant
- Conduct initial intervention session

Confirm participant ID

Check to be sure that the correct participant ID label has been attached to the Randomization Checklist and any other forms to be used at this visit.

Confirm that the Pre-Randomization Checklist has been completed and entered

Make sure that the Pre-Randomization Checklist (Form #19) has been completed and entered. If it is not complete, finish the remaining items at this visit or reschedule a new randomization visit. All required items must be entered before the participant can be randomized.

Use the Ready for Randomization Report (MANAGE08) to confirm that all required data has been entered before proceeding with the randomization visit.

Check visit window

Make sure that the date of the Randomization/Intervention visit is within the window for the participant. The Ready for Randomization Report lists the date range appropriate for each participant. Since window is a maximum range (6 months) from SV1, this should be checked in advance of the visit. Once this visit window is exceeded it is too late to adjust the date.

Review study and confirm interest

Briefly describe PREMIER again, emphasizing the commitment required of participants. Give participant the SV3 Activity Fact Sheet (Form #107) as a visual reminder of the commitment she is being asked to make. Stress how important it is that those who enroll in the study follow through and complete the study, and confirm that participant thinks she would like to participate if eligible.

Review participant's current health status

Ask the participant whether there have been any important changes in their health status that may affect their ability to participate in the study. New injuries, surgeries, or recent major illnesses are examples of events that may influence the participant's ability to participate. If the answer is "Yes," a case conference should be conducted to assess whether the participant is a good candidate for randomization. If the case conference confirms that the participant should continue, check "Yes." If the participant is not cleared to continue, check "No," and complete Form #28 for the participant and do not enter Form #60.

Obtain consent for main trial (if not yet obtained)

Consent to participate in the main trial must be obtained sometime between the SV3 visit and prior to randomization. If this has not yet occurred, then it must be obtained now.

Measure fourth baseline blood pressure (if not yet obtained)

In addition to the three eligibility blood pressure measurements taken at SV1, SV2, and SV3, all participants must provide a fourth, noneligibility baseline blood pressure measurement. This may be obtained any time after the SV3 visit and prior to randomization. If this has not yet occurred, then it must take place at the R/I visit and prior to randomization.

Take the participant's blood pressure using the random zero sphygmomanometer and the procedures described in MOP Chapter 17 (Blood Pressure Assessment). The cuff size must be the same as that used at SV1, except as noted in Chapter 17. If it is impossible to get an accurate measurement (e.g., if large cuff covers the antecubital fossa or arm circumference is >52 cm) the participant is excluded.

Although this blood pressure measurement is not intended as an eligibility measurement, participants with escape blood pressures at this visit are still excluded from the study and referred to a physician for further evaluation within one week. The escape blood pressure criteria for this visit is based only on the BP measurements taken at this visit, and not on the cumulative blood pressure measurements to date. The BP escape criterion for this visit is defined as either the sum of two systolic blood pressures exceeding 359 mm Hg or the sum of the two diastolic blood pressures exceeding 219 mm Hg. If an escape level is reached, the Blood Pressure Escape Form—Screening (Form #32) also needs to be completed, with one copy placed in the participant's chart at the site and one copy sent to the CC.

Measure waist circumference (if not yet obtained)

Measure the participant's waist circumference per the protocol outlined in MOP Chapter 20. Note the measurements on the Randomization Checklist (Form #60) in centimeters to the nearest 0.1 cm.

Weigh participant

Measure the participant's weight per the protocol outlined in MOP Chapter 20. Note the weight on the Randomization Checklist (Form #60). All weights are measured and recorded in pounds to the nearest 0.25 pounds.

Record events and final eligibility status on the Randomization Checklist

Review the Randomization Checklist and all other forms to make sure the data collection is complete, and each item has been checked off on the checklist.

Randomize participant

An unblinded staff member randomizes the participant and prints a report using the Intervention Application on the PREMIER computer workstation. The process is as follows:

(1) Open the Intervention Application and click on the Randomization button.
(2) Select Enter Randomization Checklist
(3) Enter the Randomization Checklist
(4) Select Randomize Participant
(5) Select the participant to randomize from the list of eligible participants.
(6) Click Print Randomization Report
(7) Deliver the printout to the interventionist who will be conducting the remainder of the R/I visit.

Participants are told to which group they have been assigned. Only unblinded staff have a level of computer access which allows them to perform the randomization procedure. Clinic personnel who perform follow-up participant measurements are blinded to intervention assignment.

Treatment allocation assignments are stratified by clinic and hypertensive status (yes/no), and within each strata are generated in blocks of varying sizes.

Ending the R/I Visit

To complete the R/I visit, do the following:

If the participant is ineligible

You may inform participants of their eligibility status and terminate the visit whenever it is clear that they are not eligible for PREMIER. Explain the reasons for ineligibility to the participant. Enter the visit outcome status onto the Randomization Checklist (Form #60).

If the participant is eligible

If participant is eligible, the clinic portion of the visit is ended when the participant is transferred to the intervention staff for randomization and the initial intervention visit.

Conduct initial intervention session

Once randomized, participants complete their initial intervention session. In order to assure blinding, this session should be conducted by a staff person who does not take post-randomization blood pressure measurements, and the session should be conducted in a setting separate from the routine clinical activities.

Details of how to conduct this session are included in the Intervention MOP.

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Participants with a newly positive Rose Angina Questionnaire at this visit must refrain from exercise until they have a stress test and approval from both their personal physician and a PREMIER clinician.
- Participants with a positive Rose Angina Questionnaire at this visit who had a positive baseline Rose Angina Questionnaire refrain from exercise until they have approval from both their personal physician and a PREMIER clinician. The decision to require a repeat stress test in this case is left to the discretion of the participant's personal physician.

Summary of changes between Version 1.1 and 1.2:

- Form #34, Brief Medication Use Questionnaire, no longer in use. Use Form #79, Follow Up Medication Use Questionnaire.
- Use Form #201, Weight Loss Medications that Affect Blood Pressure, when completing Form #79, Follow-Up Medication Use Questionnaire.
- If Follow-Up Symptoms Questionnaire (Form #78) Question #15 = yes, an AE Form (#30) is required.

Summary of changes between Version 1.2 and 1.3:

Form #83 is completed for 3-month BP escape tracking.

12. 3-Month Visit

Overview

This chapter describes the sequence of activities that comprise the 3-month visit. The purpose of the 3-month visit is to collect information regarding blood pressure, weight, medication use and symptoms and intervention side effects reported by participants. The blood pressure measurement is used for safety monitoring.

Setting

The 3-month visit takes place at the clinical center and requires a quiet, private or semi-private setting where the participant can wait relaxed prior to the random zero blood pressure measurement. Questionnaires also need to be administered and reviewed in a setting that permits privacy for the participant. If unable to complete a clinic visit, collect questionnaire data over the phone.

Required Materials

- 3-Month Visit Form (#56)
- Study charts for scheduled participants
- Scale

Questionnaires and Forms

- Rose Angina Questionnaire (Form #6)
- Follow-Up Symptoms Questionnaire (Form #78)
- Follow-Up Medication Use Questionnaire (Form #79)
- Weight Loss Medications that Affect Blood Pressure (Form #201)
- Adverse Events Form (#30) (if any)

Blood pressure assessment and BP forms

- Random zero sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- 3 month visit blood pressure form (Form #33)
- Blood Pressure Escape Form – 3month visits (Form #83)

Preprinted ID labels should be available to use on the forms. The number of forms and pieces of equipment are determined by local staffing configurations and the anticipated participant flow. If available, a spare (back up) sphygmomanometer should be accessible.

Conducting the 3-Month Visit

The 3-month visit should be completed between the second and fourth months post randomization. The exact sequence for the activities is left to the discretion of the individual clinical centers. The only requirement is that the visits fall within the windows shown in table 12-1. For most activities, the separate target, allowable, and adjudication windows are listed. In addition, a Visit Windows Report for each participant can be printed from the Data Management System. This gives exact calendar dates for each of the windows based on the participant's randomization date. Staff should always attempt to schedule activities to occur within the target windows, and the CC will report on the success of each site in achieving these target ranges. However measurements may still be collected outside of the target window provided that they fall within the allowable or adjudication window range. Measurements taken outside of the allowable windows are evaluated by the adjudication committee to determine if and how they can be used. It is critical that staff make every possible effort to make sure all of the three month activities occur within the allowable window.

- Confirm participant ID
- Complete the Follow-Up Symptoms Questionnaire (Form #78)
- Complete the Follow-Up Medication Use Questionnaire (Form #79)
- Complete the Rose Angina Questionnaire (Form #6)
- Measure Blood Pressure (two measurements on a single collection day)
- Measure Weight
- Record events on the 3-Month Visit Form (#56)

Table 12-1. 3 Month Visit Measurement Targets and Windows
(exact visit windows vary by participant, print Visit Window Report in Data Management System to get participant-specific dates)

RZ BP (2 times on a single collection day) **Questionnaires** **Weight**
Target • 3 months from randomization date +/- 2 weeks. *Allowable Window* • 3 months from randomization date +/- 4 weeks *Adjudication Window** • between randomization date and 5 ½ months.
**If outside allowed range, collect data, enter forms, and adjudication committee will determine if/how to use. If outside adjudication range, collect but do not enter. Adjudication committee will review.*

Confirm participant ID

Make sure that the participant's ID is on the 3-Month Visit Form and any other forms to be completed as part of the 3-month visit. Clinical center staff should confirm the accuracy of all IDs. Use of preprinted ID labels is recommended.

Administer the Follow-Up Symptoms Questionnaire (Form #78)

Ask the participant to complete the Follow-Up Symptoms Questionnaire (Form #78). If the participant answers "yes" to question #15, an Adverse Events Form (#30) is required. Check the appropriate box on the 3 Month Visit Form to indicate that the Follow-Up Symptoms Questionnaire was administered.

Complete the Follow-Up Medication Use Questionnaire (Form #79)

Confirm that the participant has brought in all medications, over-the-counter products, or nutritional supplements that they are currently using. Check the participant's medication containers and complete the Follow-Up Medication Use Questionnaire. If the participant has started taking any exclusionary medications, or any medications for which the category is unclear, a PREMIER clinician must review the form. If the participant fails to bring her current medications, it will be necessary to call the participant at home to review her medications. Use Form #201, Weight Loss Medications that Affect Blood Pressure, to check weight loss medications.

Complete Rose Angina Questionnaire (Form #6)

Administer the Rose Angina Questionnaire (Form #6) to the participant. Individuals with a positive Rose Angina Questionnaire (question #8 answered "positive") are immediately referred to their personal physician for evaluation.

If the baseline Rose Angina Questionnaire was **negative**, the participant is asked to refrain from further exercise until they have a stress test, and approval from both their personal physician and the PREMIER clinician.

If the baseline Rose Angina Questionnaire was **positive**, the participant is asked to refrain from further exercise until they have approval from both their personal physician and a PREMIER clinician. A repeat stress test is not automatically required in this case; the decision to perform one is left to the discretion of the participant's personal physician. If the participant does not have a personal physician, she is given a referral to a physician whom she is advised to consult.

In either case, if angina is confirmed, they are advised to follow their physician's advice regarding exercise. Otherwise, they can restart exercise per PREMIER recommendations.

An AE form is to be completed if the answer to question #8 is "positive."
Check the appropriate box on the 3 Month Visit Form (#56) to indicate that the Rose Angina Questionnaire was administered. Use the worksheets attached to the Rose Questionnaire to document the follow-up process.

Measure blood pressure

Two blood pressure measurements must be obtained on a single collection day between 2 and 4 months after the randomization visit. Take the participant's blood pressure using the random zero sphygmomanometer and the procedures described in MOP Chapter 17 (Blood Pressure Assessment). **Be sure to re-measure the cuff size.** Record the outcome of the measures on the 3 Month Visit Blood Pressure Form (#33).

If the mean blood pressure from these two readings is $\geq$ either SBP of 160 mmHg or DBP of 100 mmHg, one additional set of RZ measurements must be obtained within one week. If the cumulative mean from the two visits is $\geq$ SBP 180 or DBP 110, the participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is $\geq$ SBP 160 or DBP 100, then the participant is referred to his/her personal physician within one month.

The timing of the referral, within one week or within one month, depends on the threshold level that is reached (see Chapter 23, Safety Monitoring). These threshold levels are also shown on the 3 Month Visit Blood Pressure Form. If the threshold levels are exceeded, the Blood Pressure Escape Form –3-Month Visits (Form #83) needs to be completed, with one copy placed in the participant's study chart and one copy sent to the CC. The participant may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment, even if the BP is lower than the above limits.

The clinical centers should endeavor to obtain four sets of end-of-intervention blood pressure measurements on all participants who meet one of the BP escape criteria. Care should be taken that this

does not delay or otherwise interfere with appropriate clinical care. Regardless of the outcome of the referral, all participants continue in the trial and get all study measurements.

Measure Weight

Measure the participant's weight according to the procedures in Chapter 20. Record on the 3 Month Visit Form (#56).

Record events and final visit outcome on the 3 Month Visit Form (#56)

Review the 3 Month Visit Form and all other forms to make sure the data collection is complete and each item has been checked off on the checklist.

Ending the 3 Month Visits

Once all items on the 3 Month Visit Form are complete, enter the following items. Be sure to enter the 3-Month Visit Form last.

- 3 Month Visit Blood Pressure Form (#33)
- Follow-Up Symptoms Questionnaire (Form #78)
- Follow-Up Medication Use Questionnaire (Form #79)
- BP Escape Form—3- Month Visits (#83) (if any)
- Adverse Events Form (#30) (if any)
- 3 Month Visit Form (#56)

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- p. 13-4: Added: Anthropometric assessments - weight (Form #57) and waist circumference (Form #57)
- Added form numbers throughout when title of form is mentioned and corrected form titles when incorrect
- Corrected form numbers throughout when incorrect
- Titles of Forms #104 and #105 changed to "Food Interview" from "Diet Recall"
- Corrected BP forms numbers
- Corrected form to use for closeout if escape BP is reached (From #28 to #37)
- Added Form #25 (Perceived Questionnaire) to list of questionnaires administered at this visit
- Study clinician does not sign Form #16. Deleted from *Administer Symptoms Questionnaire*
- AE form is filled out if Form #16, Question #17 is "yes" (not question #14)
- AE form is filled out if Form #6, Question #8 is "positive"
- Added sentence that staff completes Form #105, Convenient Times Schedule, in section on completion of 24-hour food interviews by Penn State.
- Corrected statement regarding continuing participation of participants who initiate antihypertensive therapy: they continue in the intervention and continue to provide all study measurements, including blood pressure. These measurements are reviewed by the adjudication committee.

Summary of changes between Version 1.1 and 1.2:

- Added statement regarding how to handle positive Rose Angina questionnaires that were positive at baseline.

Summary of changes between Version 1.2 and 1.3:

- Corrected instructions for follow-up of Rose Angina Questionnaires: Participants with a newly positive Rose Angina Questionnaire at this visit must refrain from exercise until they have a stress test and approval from both their personal physician and a PREMIER clinician.
- Participants with a positive Rose Angina Questionnaire at this visit who had any previous positive Rose Angina Questionnaire refrain from exercise until they have approval from both their personal physician and a PREMIER clinician. The decision to require a repeat stress test in this case is left to the discretion of the participant's personal physician.

Summary of changes between Version 1.3 and 1.4:

- Form #11, Medication Use Questionnaire, is no longer in use for follow-up visits. Use Form #79, Follow-Up Medication Use Questionnaire.
- Complete Form #79 at every BP visit.
- Use Form #201, Weight Loss Medications that Affect Blood Pressure, when completing form #79, Follow-Up Medication Use Questionnaire.
- Weight is measured at the first visit of the cluster
- The Follow-Up Symptoms Questionnaire (Form #78) is administered at only one of the 4 cluster visits.

Summary of Edits

Summary of changes between Version 1.3 and 1.4 (continued):

- An AE Form (#30) is completed if Follow-Up Symptoms Questionnaire (Form #78) Question #15 = yes.
- For cohorts 2-4, collect additional blood for folate, carotenoids, and Vitamin B12 to be analyzed at CDC
- A blood pressure measurement that is taken as part of the BP escape procedure may be counted as the next "cluster visit" blood pressure measurement for that participant.
- If a follow-up measurement triggers a referral and the participant is not put on blood pressure medications, try to get at least one additional blood pressure measurement in order that the gap between the first and last blood pressures is at least one month.

Summary of changes between Version 1.4 and 1.5

- Reduce the number of 6-month blood pressure measurements from four sets of two to three sets of two

13. 6-Month Visit

Overview

This chapter describes the sequence of activities that comprise the 6-month "visit." Although we use the term "visit" for simplicity, these activities are actually spread out over a series of at least three visits occurring between 5 ½ and 8 ½ months post randomization.

The purpose of the 6-month visit is to collect the primary study outcomes. Additionally, data collected at the 6-month visit is used for ongoing safety monitoring.

Setting

With the possible exception of the submaximal treadmill test, which may take place at a separate medical facility, all of the 6-month measurements take place at the clinical center and require a quiet, private or semi-private setting where the participant can wait relaxed prior to the random zero blood pressure measurement. Questionnaires also need to be administered and reviewed in a setting that permits privacy for the participant.

Required Materials

- 6 Month Visit Form (#57)
- Study charts for scheduled participants
- Scale
- Tape Measure

Food Interview materials

- Food Interview Instruction Sheet (Form #104)
- Informational Poster
- Food Interview Convenient Times Schedule (Form #105)

Questionnaires

- Quality of Life Questionnaire (Form #23)
- Perceived Stress Questionnaire (Form #25)
- Exercise Confidence Questionnaire (Form #45)
- Eating Habits Confidence Questionnaire (Form #46)
- Social Support and Eating Habits Questionnaire (Form #47)
- Social Support and Exercise Habits Questionnaire (Form #48)
- Perceived Body Image Questionnaire (Form #49)
- Alcohol Intake Questionnaire (Form #22)

- Rose Questionnaire — Angina (Form #6)
- Follow-Up Symptoms Questionnaire (Form #78)
- 7-Day Physical Activity Recall (Form #18)
- Follow-Up Medication Use Questionnaire (Form #79)
- Weight Loss Medications that Affect Blood Pressure (Form #201)

Treadmill Fitness Test
(Detailed information on conducting the fitness test is included in Chapter 18, Fitness).

- Treadmill equipment and materials as specified in Chapter 18.
- Fitness Test Form (Form #26)

Central Lab Specimens Collection
(Detailed information on processing lab samples is included in Chapter 21, Central Laboratory Procedures).

- Fasting blood sample kit (analyzed centrally for total cholesterol, LDL-C, HDL-C, VLDL-C, triglycerides, insulin, glucose, and homocysteine)
- CDC kit for folate, carotenoids, vitamin B12
- 24-hr urine processing materials (analyzed centrally for Na, K, phosphorous, creatinine, and nitrogen)
- Central Lab Collection Form – 24hr Urine (Form #62 and Form #68)
- Central Lab Collection Form – Fasting Blood (Form #63 and #65)
- CDC Lab Collection Form – Folate/Carotenoid/VitB12 (Form #77)

Blood pressure assessment

- Random zero sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- 6-Month Visit Blood Pressure Forms (#67-69)
- Blood Pressure Escape Form – 6, 18 month visits (Form #52)

Anthropometric assessments

- Weight (Form #57)
- Waist circumference (Form #57)

Other Questionnaires

- Adverse Events Form (Form #30)

Preprinted ID labels should be available to use on the forms. The number of forms and pieces of equipment are determined by local staffing configurations and the anticipated participant flow. If available, a spare (back up) sphygmomanometer should be accessible.

Conducting the 6-Month Visit(s)

As noted previously, the following activities should be completed between 5 ½ and 8 ½ months post randomization. The exact sequence for the activities, however, as well as the content of any given visit, are left to the discretion of the individual clinical centers The only requirement is that the visits fall within the windows shown in table 13-1. For most activities, the separate target, allowable, and adjudication windows are listed. In addition, a Visit Windows Report for each participant can be printed from the Data Management System. This gives exact calendar dates for each of the windows based on the participant's randomization date. Staff should always attempt to schedule activities to occur within the target windows, and the CC will report on the success of each site in achieving these target ranges. However, measurements may still be collected outside of the target window provided that they fall within the allowable window range. Measurements taken outside of the allowable windows are evaluated by the adjudication committee to determine if and how they can be used. It is critical that staff make every possible effort to make sure all of the six-month activities occur within the allowable window.

- Confirm participant ID
- Complete the Follow-Up Symptoms Questionnaire (Form #78)
- Complete the Follow-Up Medication Use Questionnaire (Form #79)
- Complete the Rose Questionnaire - Angina (Form #6)
- Complete the 7-Day Physical Activity Recall (Form #18)
- Complete/review the various psychosocial questionnaires and the Alcohol Intake Questionnaire (Forms #45-49, #22 & #23)
- Collect and process the 24-hour urine specimen (Form # 62)
- Collect and process the fasting blood sample (Forms #63 and #77)
- Complete two 24-hour food interviews (by a central diet assessment center)
- Conduct the Treadmill Fitness Test and record the results (Form #26)
- Measure Blood Pressure on Three Separate Occasions (Forms #67-69)
- Measure Weight and Waist Circumference (Form #57)
- Record events on the 6-Month Visit Form (Form # 57)

Table 13-1. 6 Month Visit Measurement Targets and Windows	
RZ BP	Total of three measurement visits with two readings per visit. No two visits less than two weeks apart. When possible, center measurements around 7 months from randomization date *Target/Allowable Window* • 5 ½ months to 8 ½ months *Adjudication Window** • 3 ½ months to 11 ½ months*
Treadmill, Lab, Questionnaires, Wt, Waist, 24 hr Food Interviews* **	May be done in separate visits *Target Window* • 7 months from randomization date ± 3 weeks *Allowable Window* • 5 ½ months to 8 ½ months *Adjudication Window** • 3 ½ months to 11 ½ months
If outside allowed range, collect data, enter forms, and adjudication committee will determine if/how to use. If outside adjudication range, collect but do not enter. Adjudication committee will review.* * Food Interviews to be completed by Penn State; instructions provided by clinical site staff*	

Confirm participant ID

Make sure that the participant's ID is on the 6-Month Visit Form (#57) and any other forms to be completed as part of the 6-Month visit. Clinical center staff should confirm the accuracy of all IDs. Use of preprinted ID labels is recommended.

Administer the Follow-Up Symptoms Questionnaire (Form #78)

Ask the participant to complete the Follow-Up Symptoms Questionnaire (Form #78). If the participant answers "yes" to question #15, an Adverse Events Form (#30) is required. Administer this questionnaire at only one of the 4 cluster visits. Check the appropriate box on the 6-Month Visit Form to indicate that the Follow-Up Symptoms Questionnaire was administered.

Complete the Follow-Up Medication Use Questionnaire (Form #79)

This form is administered at every blood pressure visit. Confirm that the participant has brought in all medications, over-the-counter products, or nutritional supplements that they are currently using. Check the participant's medication containers and complete the Follow-Up Medication Use Questionnaire (Form #79). If the participant has started taking any additional medications, a PREMIER clinician must review the form. If the participant fails to bring her current medications, it will be necessary to call the participant at home to review her medications. Use Form #201, Weight Loss Medications that Affect Blood Pressure, to check weight loss medications.

Complete Rose Angina Questionnaire (Form #6)

Administer the Rose Angina Questionnaire (Form #6) to the participant. Individuals with a positive Rose Angina Questionnaire (question #8 answered "positive") are immediately referred to their personal physician for evaluation.

If **all previous** Rose Angina Questionnaires were negative, the participant is asked to refrain from further exercise until they have a stress test, and approval from both their personal physician and the PREMIER clinician.

If **any previous** Rose Angina Questionnaire was positive, the participant is asked to refrain from further exercise until they have approval from both their personal physician and a PREMIER clinician. A repeat stress test is not automatically required in this case; the decision to perform one is left to the discretion of the participant's personal physician. If the participant does not have a personal physician, she is given a referral to a physician whom she is advised to consult.

In either case, if angina is confirmed, they are advised to follow their physician's advice regarding exercise. Otherwise, they can restart exercise per PREMIER recommendations.

An AE form is to be completed if the answer to question #8 is "positive." Check the appropriate box on the 6 Month Visit Form (#57) to indicate that the Rose Angina Questionnaire was administered. Use the worksheets attached to the Rose Questionnaire to document the follow-up process.

Administer 7-Day Physical Activity Recall (Form #18)

Staff are specially trained to administer this form. Complete the 7-Day Physical Activity Recall (Form #18). Check the appropriate box on the 6-Month Visit Form indicating the recall was completed. See Chapter 22 for more details.

Complete/review the various psychosocial questionnaires and the alcohol intake questionnaire

A number of self-administered questionnaires must be completed during the 6-month visit window period. These include an alcohol intake questionnaire (Form #22) and six psychosocial questionnaires (Forms # 45-49, #23). These may either be completed at home and brought to the clinic, or else completed in the clinic. In either case clinic staff should review all of the forms for completeness and resolve any missing or ambiguous responses.

Collect the 24-hour urine sample (Form #62)

In order to maximize quality control for urine collections, the collections should ideally begin on a Monday through Thursday when the participants come in to pick up their collection materials, and

participants should be instructed to return the collections the next day. This enhances the likelihood that the initial voiding to start the interval is discarded and that a final voiding is obtained at the end of the collection interval. It should also maximize the likelihood that the collection duration falls within the allowable limits (22-26 hours). If, in the opinion of clinic staff, the participant is unlikely to comply with the collection regimen due to this weekday collection, the participant may be allowed to collect the specimen over the weekend. In this case it is still preferable to either begin or end the collection in the clinic, so that at least some level of quality assurance is achieved.

To begin the collection, distribute the 24-hour urine container and instructions to the participant and review the instructions. Stress the importance of strictly adhering to the collection protocol, and remind the participant that the sample needs to be returned to the clinic within 24 hours of the final voiding. Begin completing Form #62.

Make sure that a label is affixed to the collection jug. Refer to the Interim Visit Chapter (Chapter 10) of the MOP for detailed instructions. (See Chapter 21, Central Lab Procedures, regarding requirements for acceptability and repeat samples and for instructions on sample handling and processing.) Note: Instruct pre-menopausal women to collect the 24-hour urine specimen when they are not menstruating.

Collect and process the 12-hour fasting blood sample (Forms #63 and #77)

Part of the 6-month visit includes a fasting blood draw. Participants should be instructed to fast for 12 hours prior to the clinic visit (an overnight fast with an early morning clinic visit is suggested for this purpose). Clinic staff should also provide the participants with light snacks and juice immediately after the blood draw.

The blood specimen should be processed immediately following collection using the procedures outlined in Chapter 21, Central Lab Procedures. See Chapter 21 regarding requirements for acceptability and repeat samples. Complete the Central Lab Collection Form (#63), and the CDC Lab Collection Form – Folate/Carotenoid/B12 (Form #77). Document the collection on the 6-Month Visit Form (#57).

Completion of two 24-hour food interviews

Two unannounced 24-hour food interviews occur between 5 ½ months and 8 ½ months post randomization. These interviews, conducted by telephone by the Diet Assessment Center of Pennsylvania State University, are meant to take place within a 3-week period on nonconsecutive days. The procedure for administration of the interviews is presented in Chapter 19. Complete Form #105, Convenient Times Schedule, for appropriate time zone. Penn State will notify the clinical centers once the two interviews have been completed so that this information can be noted in the data management system using Form #57.

Conduct the treadmill fitness test and record the results

Baseline cardiorespiratory fitness is determined by submaximal treadmill stress testing. (This procedure is described in Chapter 18). Note the completed test on Form #57.

Measure blood pressure on three separate occasions
Three random zero blood pressure measurements must be obtained between 5 ½ months and 8 ½ months after the randomization visit. No two sets of measurements may be less than two weeks apart. It is recommended that timing of these measurements center around 7 months from the randomization date.

Take the participant's blood pressure using the random zero sphygmomanometer and the procedures described in MOP Chapter 17 (Blood Pressure Assessment). **Re-measure the cuff size for the first of the three measurements of the cluster. Be sure to use this same cuff size for all measurements in this cluster.** Record the outcome of the measures on the 6-Month Visit Blood Pressure Form (#53).

If the mean blood pressure recorded at any single visit is $\geq$ either SBP of 160 mmHg or DBP of 100 mmHg, one additional set of RZ measurements must be obtained within one week. If the cumulative mean from the two visits is $\geq$ SBP 180 or DBP 110, the participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is $\geq$ SBP 160 or DBP 100, then the participant is referred to his/her personal physician within one month. If the cumulative mean blood pressure recorded at the end of the three six month visits > either a SBP of 140 mmHg or a DBP or 90 mmHg, participant is referred to his/her personal physician within two months.

A blood pressure measurement that is taken as part of the BP escape procedure may be counted as the next "cluster visit" blood pressure measurement for that participant. Note that the reports showing progress through the 6-month visit will not include BP measurements that are done as part of the escape procedure. For this reason, sites must track this locally. If the follow-up measurement triggers a referral and the participant is not put on blood pressure medications, try to get at least one additional blood pressure measurement, even if you have already obtained a full set of end-of-study blood pressures, in order that the gap between the first and last blood pressures is at least one month.

The timing of the referral, within one week, within one month, or within 2 months, depends on the threshold level that is reached (see Chapter 23, Safety Monitoring). These threshold levels are also shown on the 6-Month Visit Blood Pressure Form. If the threshold levels are exceeded, the Blood Pressure Escape Form –6, 18 Month Visits (Form #52) needs to be completed, with one copy placed in the participant's study chart and one copy sent to the CC. The participant may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment even if the BP is lower than the above limits.

Participants who initiate antihypertensive therapy as a result of hitting an escape level, or for any other reason, continue in the intervention and continue to provide all study measurements, including blood pressure. The adjudication committee makes a determination as to how subsequent measurements

should be used for analysis. Enter the 6-Month Visit Blood Pressure Form (#53), and, if applicable, a BP Escape Form—6, 18 Month Visits (Form #52).

Measure Weight and Waist Circumference

At the first visit of the cluster, measure the participant's weight and waist circumference according to the procedures in Chapter 20. Record on the 6-Month Visit Form (#57).

Record events and visit outcome on the 6-Month Visit Form (#57)

Review the 6-Month Visit Form and all other forms to make sure the data collection is complete and each item has been checked off on the checklist.

Ending the 6-Month Visit(s)

Once all items on the 6 Month Visit Form are complete, enter the following items. The order of entry is not important, except that the 6-Month Visit Form must be entered last.

- 6-Month Visit Blood Pressure Form (#67-69)
- BP Escape Form—6, 18 Month Visits (#52) (if any)
- Rose Questionnaire—Angina (Form #6)
- Follow-Up Symptoms Questionnaire (Form #78)
- Adverse Events Form (#30) (if any)
- Central Lab Collection Form—6-Month 24hr Urine (Form #62)
- Central Lab Collection Form—6-Month Fasting Blood (Form #63)
- CDC Lab Collection Form – Folate/Carotenoid/B12 (form #77)
- Fitness Test Form (#26)
- 7-Day Physical Activity Recall (Form #18)
- Follow-Up Medication Use Questionnaire (Form #79)
- Quality of Life Questionnaire (Form #23)
- Perceived Stress Questionnaire (Form #25)
- Exercise Confidence Questionnaire (Form #45)
- Eating Habits Confidence Questionnaire (Form #46)
- Social Support and Eating Habits Questionnaire (Form #47)
- Social Support and Exercise Habits Questionnaire (Form #48)
- Perceived Body Image Questionnaire (Form #49)
- Alcohol Intake Questionnaire (Form #22)
- 6-Month Visit Form (#57)

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Re-organization of bulleted list on page 14-3 to be consistent with 13-3.
- Added form numbers throughout when title of form is mentioned and corrected form titles when incorrect
- Changed +/- to ±
- Study clinician does not sign Form #16. Deleted from *Administer Symptoms Questionnaire*
- AE form is filled out if Form #16, Question #17 is "yes" (not question #14)
- AE form is filled out if Form #6, Question #8 is "positive"

Summary of changes between Version 1.1 and 1.2:

- Participants with a newly positive Rose Angina Questionnaire at this visit must refrain from exercise until they have a stress test and approval from both their personal physician and a PREMIER clinician.
- Participants with a positive Rose Angina Questionnaire at this visit who had any previous positive Rose Angina Questionnaire refrain from exercise until they have approval from both their personal physician and a PREMIER clinician. The decision to require a repeat stress test in this case is left to the discretion of the participant's personal physician.

Summary of changes between Version 1.2and 1.3:

- Form #34, Brief Medication Use Questionnaire, is no longer in use. Use Form #79, Follow-Up Medication Use Questionnaire.
- Use Form #201, Weight Loss Medications that Affect Blood Pressure, when completing Form #79, Follow-Up Medication Use Questionnaire
- If Follow-Up Symptoms Questionnaire (Form #78) Question #15 = yes, an AE Form (330) is required.

Summary of changes between Version 1.3and 1.4:

- Form #84 is completed for 12-month BP escape tracking.

14. 12-Month Visit

Overview

This chapter describes the sequence of activities that comprise the 12-month visit. The purpose of the 12-month visit is to collect information regarding blood pressure, weight, medication use and symptoms and intervention side effects reported by participants. The blood pressure measures act as a safety check required periodically throughout the study.

Setting

All of the 12-month measurements take place at the clinical center and require a quiet, private or semi-private setting where the participant can wait relaxed prior to the random zero blood pressure measurement. Questionnaires also need to be administered and reviewed in a setting that permits privacy for the participant.

Required Materials

- 12-Month Visit Form (#58)
- Study charts for scheduled participants
- Scale

Questionnaires

- Rose Angina Questionnaire (Form #6)
- Follow-Up Symptoms Questionnaire (Form #78)
- Follow-Up Medication Use Questionnaire (Form #79)
- Weight Loss Medications that Affect Blood Pressure (Form #201)

Blood pressure assessment

- Random zero sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- 12 month visit blood pressure form (Form #54)
- Blood Pressure Escape Form –12 month visits (Form #84)

Preprinted ID labels should be available to use on the forms. The number of forms and pieces of equipment are determined by local staffing configurations and the anticipated participant flow. If available, a spare (back up) sphygmomanometer should be available.

Conducting the 12-Month Visit

As noted previously, the following activities should be completed between 11 and 13 months post randomization. The exact sequence for the activities, however, as well as the content of any given visit, are left to the discretion of the individual clinical centers. The only requirement is that the visits fall within the windows shown in table 14-1. For most activities, the separate target, allowable, and adjudication windows are listed. In addition, a Visit Windows Report for each participant can be printed from the Data Management System. This gives exact calendar dates for each of the windows based on the participant's randomization date. Staff should always attempt to schedule activities to occur within the target windows, and the CC will report on the success of each site in achieving these target ranges. However measurements may still be collected outside of the target window provided that they fall within the allowable window range. Measurements taken outside of the allowable windows are evaluated by the adjudication committee to determine if and how they can be used. It is critical that staff make every possible effort to make sure all of the three month activities occur within the allowable window.

- Confirm participant ID
- Complete the Rose Questionnaire – Angina (Form #6)
- Measure Blood Pressure (two measurements on a single collection day) (Form #54)
- Measure Weight (Form #58)
- Complete the Follow-Up Symptoms Questionnaire (Form #78)
- Complete the Follow-Up Medication Use Questionnaire (Form #79)
- Record events on the 12-Month Visit Form (#58)

Table 14-1. 12 Month Visit Measurement Targets and Windows
(exact visit windows vary by participant, print Visit Window Report in Data Management System to get participant-specific dates)

RZ BP (2 times on a single collection day) **Questionnaires** **Weight**
Target • 12 months from randomization date $\pm$ 2 weeks. *Allowable Window* • 12 months from randomization date $\pm$ 4 weeks *Adjudication Window** • between 7 ½ months and 15 ½ months.
**If outside allowed range, collect data, enter forms, and adjudication committee will determine if/how to use. If outside adjudication range, collect but do not enter. Adjudication committee will review.*

Confirm participant ID

Make sure that the participant's ID is on the 12-Month Visit Checklist and any other forms to be completed as part of the 12-month visit. Clinical center staff should confirm the accuracy of all IDs. Use of preprinted ID labels is recommended.

Complete Rose Angina Questionnaire (Form #6)

Administer the Rose Angina Questionnaire (Form #6) to the participant. Individuals with a positive Rose Angina Questionnaire (question #8 answered "positive") are immediately referred to their personal physician for evaluation.

If **all previous** Rose Angina Questionnaires were negative, the participant is asked to refrain from further exercise until they have a stress test, and approval from both their personal physician and the PREMIER clinician.
If **any previous** Rose Angina Questionnaire was positive, the participant is asked to refrain from further exercise until they have approval from both their personal physician and a PREMIER clinician. A repeat stress test is not automatically required in this case; the decision to perform one is left to the discretion of the participant's personal physician. If the participant does not have a personal physician, she is given a referral to a physician whom she is advised to consult.

In either case, if angina is confirmed, they are advised to follow their physician's advice regarding exercise. Otherwise, they can restart exercise per PREMIER recommendations.

An AE form is to be completed if the answer to question #8 is "positive." Check the appropriate box on the 18 Month Visit Form (#58) to indicate that the Rose Angina Questionnaire was administered. Use the worksheets attached to the Rose Questionnaire to document the follow-up process.

Measure blood pressure (Form #54)

Two blood pressure measurements must be obtained on a single collection day between 11 and 13 months after the randomization visit. Take the participant's blood pressure using the random zero sphygmomanometer and the procedures described in MOP Chapter 17 (Blood Pressure Assessment). **Be sure to re-measure the cuff size.** Record the outcome of the measures on the 12 Month Visit Blood Pressure Form (#54).

If the mean blood pressure from these two readings is $\geq$ either SBP of 160 mmHg or DBP of 100 mmHg, one additional set of RZ measurements must be obtained within one week. If the cumulative mean from the two visits is $\geq$ SBP 180 or DBP 110, the participant is referred to his/her personal

physician for further evaluation within one week. If the cumulative mean from the two visits is ≥ SBP 160 or DBP 100, then the participant is referred to his/her personal physician within one month.

If the cumulative mean blood pressure recorded at the 12 month visit is ≥ either a SBP of 140 mmHg or a DBP of 90 mmHg, one additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is ≥ SBP 160 or DBP 100, the participant is referred to his/her personal physician within one month. If the cumulative mean from the two visits is ≥ SBP140 or DBP 90, the participant is referred to a physician for further evaluation within two months.

The timing of the referral, within one week, within one month, or within two months, depends on the threshold level that is reached (see Chapter 23, Safety Monitoring). These threshold levels are also shown on the 12 Month Visit Blood Pressure Form. If the threshold levels are exceeded, the Blood Pressure Escape Form –12 Month Visits (Form #84) needs to be completed, with one copy placed in the participant's study chart and one copy sent to the CC. The participant may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment even if the BP is lower than the above limits.

The clinical centers should endeavor to obtain four sets of end-of-intervention blood pressure measurements on all participants who meet one of the BP escape criteria. Care should be taken that this does not delay or otherwise interfere with appropriate clinical care. Regardless of the outcome of the referral, all participants continue in the trial and get all study measurements.

Measure weight

Measure the participant's weight according to the procedures in Chapter 20. Record on the 12 Month Visit Form (#58).

Administer the Follow-Up Symptoms Questionnaire (Form #78)

Ask the participant to complete the Follow-Up Symptoms Questionnaire (Form #78). If the participant answers "yes" to question #15, an Adverse Events Form (Form #30) is required. Check the appropriate box on the 12 Month Visit Form to indicate that the Follow-Up Symptoms Questionnaire was administered.

Complete the Follow-Up Medication Use Questionnaire (Form #79)

Confirm that the participant has brought in all medications, over-the-counter products, or nutritional supplements that they are currently using. Check the participant's medication containers and complete the Follow-Up Medication Use Questionnaire. If the participant has started taking any exclusionary medications, or any medications for which the category is unclear, a PREMIER clinician must review the form. If the participant fails to bring her current medications, it will be necessary to call the participant at home to review her medications. Use Form #201, Weight Loss Medications that Affect Blood Pressure, to check weight loss medications.

Record events and final eligibility status on the 12 Month Visit Form (#58)

Review the 12 Month Visit Form and all other forms to make sure the data collection is complete and each item has been checked off on the checklist.

Ending the 12 Month Visit

Once all items on the 12 Month Visit Form are complete, enter the following items. Be sure to enter the 12 Month Visit Form last.

- BP Escape Form—12 Month Visits (#84) (if any)
- Follow-Up Symptoms Questionnaire (Form #78)
- Participant Closeout Form (#28) (if any)
- Adverse Events Form (#30) (if any)
- Follow-Up Medication Use Questionnaire (Form #79)
- 12 Month Visit Form (#58)

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Form #11, Medication Use Questionnaire, is no longer in use for follow-up visits. Use Form #79, Follow-Up Medication Use Questionnaire.
- Complete Form #79 at every BP visit.
- Use Form #201, Weight Loss Medications that Affect Blood Pressure, when completing Form #79, Follow-Up Medication Use Questionnaire.
- Weight is measured at the first visit of the cluster.
- The Follow-Up Symptoms Questionnaire (Form #78) is administered at only one of the 4 cluster visits.
- If the Follow-Up Symptoms Questionnaire (Form #78), Question #15 = yes, an AE Form (#30) is required.
- For cohorts 2-4, collect additional blood for folate, carotenoids, and vitamin B12 to be analyzed at CDC.
- A blood pressure measurement that is taken as part of the BP escape procedure may be counted as the next "cluster visit" blood pressure measurement for that participant.
- If a follow-up measurement triggers a referral and the participant is not put on blood pressure medications, try to get at least one additional blood pressure measurement in order that the gap between the first and last blood pressures is at least one month

Summary of changes between Version 1.1 and 1.2:

- Homocysteine is not collected at the 18-month visit
- Reduce the number of 18-month blood pressure measurements from four sets of two to three sets of two.

15. 18-month Visit

Overview

This chapter describes the sequence of activities that comprise the 18-month "visit." Although we use the term "visit" for simplicity, these activities are actually spread out over a series of at least three visits occurring between 15½ and 18½ months post randomization.

The purpose of the 18-month visit is to collect the secondary study outcomes. Data collected at the 18-month visit are also used for ongoing safety monitoring. Additionally, study closeout occurs after all data have been collected.

Setting

With the possible exception of the submaximal treadmill test, which may take place at a separate medical facility, all of the 18-month measurements take place at the clinical center and require a quiet, private or semi-private setting where the participant can wait relaxed prior to the random zero blood pressure measurement. Questionnaires also need to be administered and reviewed in a setting that permits privacy for the participant.

Required Materials

- 18-month Visit Form (Form #59)
- Study charts for scheduled participants
- Scale
- Tape Measure

Food Interview materials

- Food Interview Instruction Sheet (Form #104)
- Informational Poster
- Food Interview Convenient Times Schedule (Form #105)

Questionnaires

- Quality of Life Questionnaire (Form #23)
- Exercise Confidence Questionnaire (Form #45)
- Eating Habits Confidence Questionnaire (Form #46)
- Social Support and Eating Habits Questionnaire (Form #47)
- Social Support and Exercise Habits Questionnaire (Form #48)
- Perceived Body Image Questionnaire (Form #49)
- Alcohol Intake Questionnaire (Form #22)
- Rose Questionnaire — Angina (Form #6)

- Follow-Up Symptoms Questionnaire (Form #78)
- 7-Day Physical Activity Recall (Form #18)
- Follow-Up Medication Use Questionnaire (Form #79)
- Weight Loss Medications that Affect Blood Pressure (Form #201)

Treadmill Fitness Test
(Detailed information on conducting the fitness test is included in Chapter 18, Fitness).

- Treadmill equipment and materials as specified in Chapter 18.
- Fitness Test Form (Form #26)

Central Lab Specimens Collection
(Detailed information on processing lab samples is included in Chapter 21, Central Laboratory Procedures).

- Fasting blood sample kit (analyzed centrally for total cholesterol, LDL-C, HDL-C, VLDL-C, triglycerides, insulin, and glucose).
- CDC kit for folate, carotenoids, and vitamin B12
- 24-hr urine processing materials (analyzed centrally for Na, K, phosphorous, creatinine, and nitrogen)
- Central Lab Collection Form—18-Month 24hr Urine (Form #64)
- Central Lab Collection Form—18-Month Fasting Blood (Form#65)
- CDC Lab Collection Form – Folate/Carotenoids/VitB12 (Form #77)

Blood pressure assessment

- Random zero sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- 18-month Visit Blood Pressure Forms (#s 71-73)
- Blood Pressure Escape Form – 6, 18 month visits (Form #52)

Anthropometric Assessments

- Weight (Form #59)
- Waist Circumference (Form #59)

Other Questionnaires

- Adverse Events Form (Form #30)

Preprinted ID labels should be available to use on the forms. The number of forms and pieces of equipment are determined by local staffing configurations and the anticipated participant flow. If available, a spare (back up) sphygmomanometer should be accessible.

Conducting the 18-month Visit(s)

As noted previously, the following activities should be completed between 15½ and 18½ months post randomization. The exact sequence for the activities, however, as well as the content of any given visit, are left to the discretion of the individual clinical centers. The only requirement is that the visits fall within the windows shown in table 15-1. For most activities, the separate target, allowable, and adjudication windows are listed. In addition, a Visit Windows Report for each participant can be printed from the Data Management System. This gives exact calendar dates for each of the windows based on the participant's randomization date. Staff should always attempt to schedule activities to occur within the target windows, and the CC will report on the success of each site in achieving these target ranges. However measurements may still be collected outside of the target window provided that they fall within the allowable window range. Measurements taken outside of the allowable windows are evaluated by the adjudication committee to determine if and how they can be used. It is critical that staff make every possible effort to make sure all of the 18-month activities occur within the allowable windows.

- Confirm participant ID
- Complete the Follow-Up Symptoms Questionnaire (Form #78)
- Complete the Follow-Up Medication Use Questionnaire (Form #79)
- Complete the Rose Questionnaire—Angina (Form #6)
- Complete the 7-Day Physical Activity Recall (Form #18)
- Complete/review the various psychosocial questionnaires and the Alcohol Intake Questionnaire (Forms #45-49, #22 & #23)
- Collect and process the 24-hour urine specimen (Form #64)
- Collect and process the fasting blood sample (Forms #65 and #77)
- Complete two 24-hour food interviews (by a central diet assessment center)
- Conduct the Treadmill Fitness Test and record the results (Form #26)
- Measure Blood Pressure on Three Separate Occasions (Forms #71-73)
- Measure Weight and Waist Circumference (Form #59)
- Record events on the 18-month Visit Form (Form #59)

Table 15-1. 18 month Visit Measurement Targets and Windows	
RZ BP	Total of three measurement visits. No two visits less than two weeks apart. When possible, center measurements around 17 months from randomization date *Target/Allowable Window* • 15 1/2 months to 18 1/2 months *Adjudication Window** • 12 1/2 months to 24 months
Treadmill, Lab, Questionnaires, Wt, Waist, 24 hr Food Interviews* **	May be done in separate visits *Target Window* • 17 months from randomization date ± 3 weeks. *Allowable Window* • 15 1/2 months to 18 1/2 months *Adjudication Window** • 12 1/2 months to 24 months
If outside allowed range, collect data, enter forms, and adjudication committee will determine if/how to use. If outside adjudication range, collect but do not enter. Adjudication committee will review.* * Food Interviews to be completed by Penn State; instructions provided by clinical site staff*	

Confirm Participant ID

Make sure that the participant's ID is on the 18-month Visit Form (Form #59) and any other forms to be completed as part of the 18-month visit. Clinical center staff should confirm the accuracy of all IDs. Use of preprinted ID labels is recommended.

Administer the Follow-Up Symptoms Questionnaire (Form #78)

Ask the participant to complete the Follow-up Symptoms Questionnaire (Form #78). If the participant answers "yes" to question #15, an Adverse Events Form (#30) is required. Check the appropriate box on the 18-month Visit Form to indicate that the Follow-Up Symptoms Questionnaire was administered. Administer this questionnaire at only one of the three cluster visits.

Complete the Follow-Up Medication Use Questionnaire (Form #79)

This form is administered at every blood pressure visit. Confirm that the participant has brought in all medications, over-the-counter products, or nutritional supplements that she is currently using. Check the participant's medication containers and complete the Follow-up Medication Use Questionnaire (Form #79). If the participant has started taking any additional medications, a PREMIER clinician must review the form. If the participant fails to bring her current medications, it will be necessary to call the participant at home to review her medications. Use Form #201, Weight Loss Medications that Affect Blood Pressure, to check weight loss medications.

Complete Rose Angina Questionnaire (Form #6)

Administer the Rose Angina Questionnaire (Form #6) to the participant. Individuals with a positive Rose Angina Questionnaire (question #8 answered "positive") are immediately referred to their personal physician for evaluation and advised to follow that physician's advice regarding further exercise. If the participant does not have a personal physician, a study clinician may make a recommendation regarding further exercise. However, the participant is also given a referral to a physician whom they are advised to consult. An AE form is to be completed if the answer to question #8 is "positive." Check the appropriate box on the 18 Month Visit Form (#59) to indicate that the Rose Angina Questionnaire was administered. Use the worksheets attached to the Rose Questionnaire to document the follow-up process.

Administer 7-Day Physical Activity Recall (Form #18)

Complete the 7-Day Physical Activity Recall (Form #18). Staff are specially trained to administer this form. Check the appropriate box on the 18-Month Visit Form indicating the recall was completed. See Chapter 22 for more details.

Complete/review the various psychosocial questionnaires and the alcohol intake questionnaire

A number of self-administered questionnaires must be completed during the 18-month visit. These include an alcohol intake questionnaire (Form #22) and various psychosocial questionnaires (Forms #45-49, #23). These may be completed at home and brought to the clinic, or else completed in the clinic. In either case, clinic staff should review all of the forms for completeness and resolve any missing or ambiguous responses.

Collect and process the 24-hour urine sample (Form #64)

In order to maximize quality control for urine collections, the collections should ideally begin on a Monday through Thursday when the participants come in to pick up their collection materials, and participants should be instructed to return the collections the next day. This enhances the likelihood that the initial voiding to start the interval is discarded and that a final voiding is obtained at the end of the collection interval. It should also maximize the likelihood that the collection duration falls within the allowable limits (22-26 hours). If, in the opinion of clinic staff, the participant is unlikely to comply with the collection regimen due to this weekday collection, the participant may be allowed to collect the specimen over the weekend. In this case it is still preferable to either begin or end the collection in the clinic, so that at least some level of quality assurance is achieved.

To begin the collection, distribute the 24-hour urine container and instructions to the participant and review the instructions. Stress the importance of strictly adhering to the collection protocol, and remind the participant that the sample needs to be returned to the clinic within 24 hours of the final voiding (48 hours if started on a Friday). Make sure that a label is affixed to the

collection jug. Refer to the Interim Visit Chapter (Chapter 10) of the MOP for detailed instructions. (Note: Instruct pre-menopausal women to collect the 24-hour urine specimen when they are not menstruating.) Complete Form #64 and document the collection on the 18-Month Visit Form (#59). (See Chapter 21, Central Lab Procedures, regarding requirements for acceptability and repeat samples. Details on handling of samples and processing are also covered in Chapter 21.)

Collect and process the 12-hour fasting blood sample (Forms #65 and #77)

Part of the 18-month visit includes a fasting blood draw. Participants should be instructed to fast for 12 hours prior to the clinic visit (an overnight fast with an early morning clinic visit is suggested for this purpose). Clinic staff should also provide the participants with light snacks and juice immediately after the blood draw. (See Chapter 21, Central Lab Procedures, regarding requirements for acceptability and repeat samples.)

The blood specimen should be processed immediately following collection using the procedures outlined in Chapter 21. Complete the Central Lab Collection Form—18-Month Fasting Blood (Form #65) and the CDC Lab Collection Form – Folate/Carotenoids/VitB12 (Form #77). Document the collection on the 18-month Visit Form (Form #59).

Completion of two 24-hour food interviews

Two unannounced 24-hour food interviews occur between 15 ½ months and 18 ½ months post randomization. These interviews, conducted by telephone by the Diet Assessment Center of Pennsylvania State University, are meant to take place within a 3-week period on nonconsecutive days. The procedure for administration of the interviews is presented in Chapter 19. Complete Form #105, Convenient Times Schedule, for appropriate time zone. Penn State will notify the clinical centers once the two interviews have been completed so that this information can be noted on the 18-month Visit Form (Form #59).

Conduct the treadmill fitness test and record the results

Baseline cardiorespiratory fitness is determined by submaximal treadmill stress testing. This procedure is described in Chapter 18. Note the completed test on the 18-month Visit Form (Form #59).

Measure blood pressure on three separate occasions

Three random zero blood pressure measurements must be obtained between 15 ½ months and 18 ½ months after the randomization visit. No two sets of measurements may be less than two weeks apart. It is recommended that timing of these measurements center around 17 months from the randomization date.

Take the participant's blood pressure using the random zero sphygmomanometer and the procedures described in MOP Chapter 17 (Blood Pressure Assessment). **Re-measure the cuff**

size for the first of the three measurements of the cluster. Be sure to use this same cuff size for all measurements in this cluster. Record the outcome of the measures on the 18-month Visit Blood Pressure Forms (#s 71-73).

If the mean blood pressure recorded at any single visit is ≥ either SBP of 160 mmHg or DBP of 100 mmHg, one additional set of RZ measurements must be obtained within one week. If the cumulative mean from the two visits is ≥ SBP 180 or DBP 110, the participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is ≥ SBP 160 or DBP 100, then the participant is referred to his/her personal physician within one month. If the cumulative mean blood pressure recorded at the end of the three 18- month visits > either a SBP of 140 mmHg or a DBP or 90 mmHg, participant is referred to his/her personal physician within two months.

A blood pressure measurement that is taken as part of the BP escape procedure may be counted as the next "cluster visit" blood pressure measurement for that participant. Note that the reports showing progress through the 18-month visit will not include BP measurements that are done as part of the escape procedure. For this reason, sites must track this locally. If the follow-up measurement triggers a referral and the participant is not put on blood pressure medications, try to get at least one additional blood pressure measurement, even if you have already obtained a full set of end-of-study blood pressures, in order that the gap between the first and last blood pressures is at least one month.

The timing of the referral, within one week, within one month, or within 2 months, depends on the threshold level that is reached (see Chapter 23, Safety Monitoring). These threshold levels are also shown on the 18-month Visit Blood Pressure Forms (#71-73). If the threshold levels are exceeded, the Blood Pressure Escape Form –6, 18 Month Visit Clusters (Form #52) needs to be completed, with one copy placed in the participant's study chart and one copy sent to the CC. The participant may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment even if the BP is lower than the above limits.

Participants who initiate antihypertensive therapy as a result of hitting an escape level, or for any other reason, continue in the intervention and continue to provide all study measurements, including blood pressure. The adjudication committee makes a determination as to how subsequent measurements should be used for analysis. Enter the 18-month Visit Blood Pressure Form (#71-73), and if applicable a BP Escape Form—6, 18 Month Visits (Form #52).

Measure Weight and Waist Circumference

At the first visit of the cluster, measure the participant's weight and waist circumference according to the procedures in Chapter 20. Record on the 18-month Visit Form (Form #59).

Record events on the 18-month Visit Form (Form #59)

Review the 18-month Visit Form and all other forms to make sure the data collection is complete and each item has been checked off on the checklist.

Ending the 18-month Visit(s)

Once all items on the 18-Month Visit Form are complete, enter the following forms. The order of entry is not important, except that the 18-Month Visit Form must be entered last.

- 18-month Visit Blood Pressure Forms (#71-73)
- BP Escape Form—6, 18 Month Visits (#52) (if any)
- Rose Questionnaire—Angina (Form #6)
- Follow-Up Symptoms Questionnaire (Form #78)
- Adverse Events Form (#30) (if any)
- Central Lab Collection Form—18-Month 24hr Urine (Form #64)
- Central Lab Collection Form—18-Month Fasting Blood (Form #65)
- CDC Lab Collection Form – Folate/Carotenoids/VitB12 (Form #77)
- Fitness Test Form (#26)
- 7-Day Physical Activity Recall (Form #18)
- Follow-Up Medication Use Questionnaire (Form #79)
- Quality of Life Questionnaire (Form #23)
- Exercise Confidence Questionnaire (Form #45)
- Eating Habits Confidence Questionnaire (Form #46)
- Social Support and Eating Habits Questionnaire (Form #47)
- Social Support and Exercise Habits Questionnaire (Form #48)
- Perceived Body Image Questionnaire (Form #49)
- Alcohol Intake Questionnaire (Form #22)
- 18-month Visit Form (Form #59)

Study close-out

Once a study participant has completed data collection for the 18-month visit, he/she will have completed the study and is ready to complete closeout procedures. Close-out will include providing clinical results as outlined in Chapter 16, and may include additional lifestyle counseling, particularly for Group A. Refer to Clinical MOP Chapter 16 and Intervention MOP Chapter 57 for detailed procedures.

Summary of Edits

Summary of changes between Version 1.0 and 1.1

- Deleted reference to pregnancy in statement regarding 4 sets of intervention blood pressures and other closeout procedures for randomized participants unable to complete the study. Participants who become pregnant do not receive any end of study measurements.

Summary of changes between Version 1.1 and 1.2

- Added table in unblinding reflecting SC decisions about when to give results and trialwide information to be given to participants

16. Participant Close-out

Purpose

This chapter contains instructions for closing out participants prior to randomization, early termination after randomization, and for closing out randomized participants at the end of the cohort.

Close out Prior to Randomization

If a participant refuses to participate in the study or becomes ineligible prior to randomization, they are closed out of the PREMIER data entry system in one of two ways.

At a screening visit: If refusal/ineligibility is determined at a screening visit, the participant can simply be closed out by marking "ineligible" or "refusal" on the bottom of the relevant screening visit form and then entering that form into the system. All completed data collection forms for that participant for that visit should be entered into the PREMIER data entry system before officially closing them out by entering the "visit outcome" into the data management system.

Between screening visits: If refusal/ineligibility is determined between screening visits, the participant can be closed out using the Participant Closeout Form (#28). For example, a participant's local lab results may be received in-between SV2 and SV3, or a participant may call in to cancel the next screening visit and refuse to participate any further. All prior screening data collection forms that have been collected should be entered before closing out the participant. Once refusal or ineligibility is determined, no additional data collection is required. The Participants in Limbo report located in the data management system can be run at any time to identify any non-randomized participants that still have an "eligible" code in the system and need to be closed out. A final status needs to be resolved for all participants on the Randomized Participants in Limbo report by the end of the each cohort.

Early Termination after Randomization

If a participant becomes pregnant during the study, she is excluded immediately from further participation in all study activities.

Participants reaching the blood pressure escape thresholds are referred to their personal physician for evaluation and possible drug treatment. If possible, before blood pressure medications are started, the clinical center should endeavor to obtain four sets of end-of-intervention blood pressure measurements on all participants who meet one of the BP escape criteria.

Participants who suffer a morbid event with lasting effect on blood pressure (e.g., myocardial infarction, stroke) may continue with the interventions and follow-up clinical visits with the

approval of their primary physician and study clinician in order to study secondary outcomes and adherence.

If a participant develops any other exclusionary condition (e.g. cancer) following randomization, further participation is determined by a study clinician in conjunction with the participant's personal physician.

Where possible, randomized individuals who are unable to complete the study for any reason (escape blood pressure, morbid event, etc.) should have 4 sets of end of intervention blood pressures, all other end of intervention measurements and receive a closeout briefing. This briefing should occur as soon after the terminating event as the participant's condition permits. However, it need not be done as a face-to-face meeting; the information may be sent by mail.

For any randomized participant who doesn't complete the intervention, the Premature Study Termination Form (#37) should be completed and entered into the PREMIER data entry system. Be sure to review the coding instructions on the Premature Termination Form for additional termination codes. If the termination reason is coded as "other", the clinic coordinator should fax a copy of the termination form to the CC data manager for review. The CC will add additional codes if necessary or recode the "other" response if possible. Also, before entering the termination form, be sure that all other remaining data has been entered.

Unblinding

Participants are told their baseline blood pressure measurements and also receive a summary of their six-month blood pressure measurements. At the conclusion of intervention (at 18 months), participants receive a complete set of blood pressure results, along with a summary of their laboratory measurements.

Information is given to participants as follows:

	Group A	**Groups B and C**
Baseline	BP, lab	BP, lab, fitness[1]
6 months	BP, lab	BP, lab, fitness[1]
18 months*	BP, lab, fitness[1], PAR, diet recall	BP, lab, fitness[1], PAR, diet recall
EOS	Trialwide data	Trialwide data

* Give comprehensive data as soon as possible after intervention (24 months for C1). Give whatever data you can immediately. Rationale for the time lag for cohort 1 is to have the feedback occur after the 6 month collection for C4.

1 This information is conveyed by an interventionist or other unblinded staff. Give baseline results at the randomization visit.

End of Cohort Close Out

This section contains instructions on the final closing out of participants from the PREMIER data management system**.**

All participants should have all data collection forms entered into the PREMIER data entry system. Next, the 18-month visit data completeness report should be run and checked to verify that all data has been entered. Finally, the 18-month Visit Form (#59) can be entered. This closes out the participant and no further data can be entered.

The Randomized Participants in Limbo report located in the data management system can be run at any time to identify any randomized participants for past cohorts that still have an "eligible" code in the system and need to be closed out. The data needs to be resolved for all participants on the Randomized Participants in Limbo report after the end of the each cohort.

Participant Closeout

End of Cohort

Refer to the INTERVENTION MOP for detailed instructions on participant closeout activities.

End of Trial

At the conclusion of the full trial, after all cohorts have been completed, study participants are informed about the overall findings of the trial.

17. BLOOD PRESSURE ASSESSMENT 4

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Deleted references to participant blinding to blood pressure measurements
- Added that master trainers are recertified centrally every 6 months
- Arm circumference is also measured at FU 6 and 18 at the first BP of the cluster

Summary of changes between Version 1.1 and 1.2:

- Minor edits and corrections to forms numbers and names
- Required length of stethoscope tubing changed from 10-12" to 18" or less
- If minimum or maximum zero level on RZ devices exceeds determined levels, notify the coordinating center.
- If the mercury column "bounces", read systolic BP at highest level, and diastolic BP at lowest level. (need to verify with AHA)
- Standard and RZ manometers and cuffs are inspected quarterly rather than bimonthly
- Observation is required if technicians take fewer than 4 readings in any 3-month interval.

Summary of changes between Version 1.2 and 1.3:

- Added instructions for obtaining blood pressure measurements when unable to hear initial reading.
- Updated master trainer certification requirements to show that once screening is completed, unblinded master trainers will recertify by using the Y-tubing procedure quarterly, since they will not be able to take follow-up blood pressure measurements on participants.
- If an anaeroid sphygmomanometer is used (at home visits only, instead of RZ or standard), quarterly inspection and annual cleaning are required of the anaeroid devices.

17. Blood Pressure Assessment

Overview

Correct measurement of blood pressure (BP) is of the utmost importance to the success of PREMIER. It is essential that the procedures described in this chapter for measuring BP be followed exactly. Precision is essential for valid comparisons of blood pressure between groups of people and in individuals on different occasions.

In PREMIER, sitting BP is measured using two readings with a random zero (RZ) sphygmomanometer. The essential distinction between the RZ and standard devices is a mechanism designed to produce a variable level of mercury in the mercury tube when the actual pressure in the cuff is zero. This is accomplished through an adjustable bellows chamber that is interconnected with the mercury reservoir at one end and the mercury tube at the other. The adjustment is made by the technician, who spins an external thumbwheel that contacts and rotates an internal, beveled cam; the position at which the cam comes to rest after spinning determines where the beveled edge will meet the movable diaphragm of the mercury chamber. When air pressure is applied through the cuff with the bellows cock in the open position, the diaphragm is displaced until it rests against the cam, and the mercury not accommodated by the new volume of the chamber is displaced into the mercury tube. The bellows cock, or valve, is controlled by the technician and locks the chamber system after the maximum inflation pressure desired has been applied, so that at the end of the reading, and only at the end, the mercury comes to rest at its "randomly" determined zero-pressure level. When this value is subtracted from the recorded readings the corrected readings give the corresponding true pressure levels. Thus, by adding this mechanism for varying the zero level of mercury, the RZ device obscures to the technician the true levels of pressure observed until after they have been read and the zero level subtracted. In this way, some of the recognized difficulties in technician performance are substantially reduced, particularly technician bias when readings fall near critical BP levels.

The procedures described herein are based on those used in the Dietary Approaches to Stop Hypertension (DASH) and the Trials of Hypertension Prevention (TOHP) studies.

Equipment Required

Stethoscope

A standard, good quality stethoscope (e.g., Littman, HP) with a bell is used. Korotkoff sounds **are best heard with the bell** because of their low pitch frequency. Stethoscope tubing should be 18 inches or less from the bell piece to the Y branching. This length provides optimal acoustic properties and allows the technician to read the sphygmomanometer at eye level in a comfortable position. Ear pieces should fit comfortably and snugly in the ears.

1. The ear pieces should be directed downward and forward into the external ear canal.

2. The ear pieces should fit tightly enough to exclude outside sound but not so tightly that they cause discomfort.
3. The valve between the bell and the diaphragm should be turned in the correct direction.
4. The bell of the stethoscope should be placed lightly on the skin overlying the brachial artery. Light pressure accentuates low-pitched sound and avoids compression murmurs. Pressing too heavily with the stethoscope over the brachial artery causes turbulent flow in the artery and results in a murmur which may prolong the apparent duration of phase 4.

Sphygmomanometers

Standard Hawksley RZ instruments are used to collect all study BPs. Standard Baum manometers are used to determine peak inflation level.

The standard mercury manometer consists of a screw cap, a face with numbers, a lined glass column, a reservoir containing mercury, rubber tubing, and a metal case. The rubber tubing from the mercury manometer connects to rubber tubing from the inflatable rubber bladder of the cuff. As the bladder is inflated, the air pressure in the bladder travels through the connecting rubber tubing and pushes the mercury out of the reservoir and into the lined glass column. The number for each line is read when the rounded top of the mercury, the meniscus, is level with it. If the meniscus is exactly between the lines, the reading is made from the line immediately above, i.e., **rounded up to the nearest even number**.

If the mercury column "bounces" with the particpant's pulse, read the systolic bp at the highest level, and read diastolic bp at the lowest level which the mercury reaches on the "bounce". The RZ manometer has all the parts of the standard mercury device. In addition, it has a device built into the box-shaped back that changes the level of mercury in the calibrated glass tube. This device includes a second mercury reservoir area, the size of which can be changed to hold a larger or smaller amount of the mercury, thus allowing different amounts of mercury to remain in the calibrated glass tube and outside reservoir. The size of the second, inner reservoir is changed by turning a wheel on the side of the box. The second reservoir opens and closes with a bellows control valve on the face of the manometer.

All sphygmomanometers used in PREMIER should be sent in for an overhaul prior to screening if they have not been used on a regular basis in the past year or if they have not been overhauled in the past 5 years.

Cuffs

Proper cuff size is essential for accurate BP measurement. Clinical centers must have four standard cuffs available: small adult, regular adult, large adult, and thigh cuff. The cuffs used must be Baumanometer calibrated V-Lok cuffs with Baum brand bladders. The range markings on

these and all commercial cuffs will overlap with the ranges PREMIER uses and do not offer a precise guideline. Therefore, all Baum cuffs used in PREMIER must be clearly marked on the inside surfaces with new range markings which correspond to the arm circumference ranges shown below for each cuff size.

Arm Circumference	Cuff Size
<24 cm	Small adult
24-32 cm	Regular Adult
33-41 cm	Large Adult
42-52 cm	Thigh

The correctly determined cuff size used to record SV1 blood pressure should be the same cuff size used to record all of a participant's blood pressure measurements during screening. The arm circumference is measured to determine cuff size. For 6 and 18 month follow-up, this is measured at the first BP of that cluster only. Round all fractions up to the next whole number (i.e. 32.1 should be coded as 33). The rounded arm circumference is recorded on the SV1 Blood Pressure Form (#02). Because of the potential change in weight or body composition between screening and follow-up, the arm circumference is measured again at FU3, FU12, and for FU6 and FU18 at first BP of cluster only, and recorded on the blood pressure form for the appropriate visit. This allows the staff to determine the correct cuff size to be used during run-in and intervention. If either SV1 cuff size was incorrectly recorded, or cuff size has simply changed between visits, alert the Coordinating Center. All blood pressure measurements should be taken with appropriate cuff size. If necessary, the Coordinating Center will adjust the data entry application to allow this.

Preparation for Blood Pressure Measurement

In relating to the PREMIER participants, remember that participation in the study is voluntary. Participants should be given a full explanation and instructions about the steps involved in BP measurement, as well as an opportunity to ask questions. Participants should be told in advance that their blood pressure readings will be available at each screening visit and at the 6 month follow-up and 18 month visits. However, they will be informed if their blood pressure exceeds the acceptable range at other visits. If a participant insists, a staff member may obtain an additional reading with a standard sphygmomanometer and inform him or her of the results. At the 3 and 12-month visits, this option should not be disclosed to participants in advance, and should be used only if they insist on knowing their blood pressure.

The setting at which BP readings are taken must be a separate, quiet room where no other activity is taking place and where temperature fluctuations are minimal. It is recommended that the room temperature be 65-75^{o} F. Clinic scheduling procedures should also establish consistent appointment times to minimize, insofar as possible, the impact of daily BP variations.

Participants should be told not to engage in vigorous exercise, ingest food or caffeine, or smoke

within a half hour of BP measurements. If a half hour has not elapsed, the BP measurements must be delayed until a half hour has passed.

Measurement Procedures

In PREMIER, BP will be measured 2 times during each designated visit. It will take approximately 15 minutes to take the readings, including an initial five-minute rest period. The BP measurements are obtained during the visit and prior to the group or individual intervention session (if one is scheduled on that same day).

Once the participant has had the procedures explained and the equipment has been checked, BP measurement begins. The following steps must be followed precisely.

The right arm should always be used for the measurements. If the participant indicates that there is a medical reason for not having BP measured on his or her right arm (such as surgery, or if the right arm is missing), reverse chairs and proceed with the left arm. Write a note on the BP form indicating that the left arm has been used. If the participant seems particularly apprehensive about the procedure, delay wrapping the cuff until after the five-minute wait. At SV1, 3 months, 6 months (cluster visit 1), 12 months, and 18 months (cluster visit 1), measure the arm circumference using the following procedure. At other visits through randomization, select the same cuff size as that used at SV1, and check for correct cuff size by using the PREMIER markings on the Baum cuff. If the index line falls on the maximum range markings, proceed to measure the arm circumference: Have participant stand erect holding the forearm horizontal at a 90^{o} angle. Arm length is measured using a measuring tape in metric units, measuring from the acromion or bony extremity of the shoulder girdle to the olecranon or tip of elbow. The midpoint is marked on the dorsal surface of the arm. Have participant relax their arm. With the participant's arm relaxed at their side, measure the arm circumference at the midpoint.

Seat the participant with the right arm on the table. The bend at the elbow (antecubital fossa) should be at heart level. Legs should be uncrossed and feet comfortably flat on the floor. If necessary, place a book, footstool, or other flat object beneath the participant's feet so that they do not dangle.

Palpate the brachial artery (just medial to and above the antecubital fossa) and mark this location for placement of the center of the bladder and stethoscope placement. Place the cuff on the right arm in the proper position. If the brachial artery is occluded by the cuff, as might happen with a very large but short arm, the participant is excluded from participating. Indicate on the appropriate form that you were unable to obtain a valid reading and note the reason.

Allow a five-minute wait before taking the BP. Conversation should be limited during this period. However, a brief explanation of the procedure can be repeated at this time, if necessary.

After five minutes, take a 30-second pulse (radial artery) and record. Then connect the cuff to a

standard mercury manometer to establish the pulse obliteration pressure. Palpate the radial pulse. Rapidly inflate the cuff to 80 mmHg and then slowly inflate it 10 mmHg at a time until the radial pulse can no longer be felt. Deflate and disconnect the cuff. Record the pulse obliteration pressure (POP).

Calculate and record the peak inflation level (pulse obliteration pressure + 60). The peak inflation level used for each BP measurement must be a minimum of 180. If the POP + 60 is not > 180, use 180 mmHg during the actual measurements and record 180 in item 1.e. on the form.

If for any reason, you are unable to get a valid reading of the blood pressure on the participant, she is to be excluded. Indicate on the SV1 Blood Pressure Form (#2) that you were not able to obtain a valid reading and note the reason.

Measurement # 1

Connect the cuff to the RZ manometer. Place ear pieces of the stethoscope in the ears with the tips down and forward. Open the bellows control valve and wait until the mercury settles. Using downstrokes only, turn the thumbwheel two or three times. NOTE: Do not spin the thumbwheel. Inflate rapidly but smoothly to the RZ peak inflation level. The eyes of the technician should be level with the mid-range of the manometer scale. Holding the pressure constant for five seconds with the bulb, close the bellows and control valve. Place the bell of the stethoscope on the brachial artery just below and not touching the cuff or tubing, and slowly deflate the cuff (2 mm per second) while listening.

Record the first and fifth phases, reading the pressure in mmHg and rounding up to the nearest even number. The first sound heard in a series of at least two sounds is recorded for systolic BP (phase 1). For diastolic BP (phase 5), record the first silence in a series of at least two silences, NOT the last sound heard. After noting the DBP, continue to deflate at 2 mmHg per second until 10 mmHg below DBP, then rapidly deflate the cuff by opening the thumb valve. If there is an absent 5th phase (sounds heard to 00 mmHg), the beginning of the 4th phase should be used. Make a note if there is an absent 5th phase. If the participant coughs or sneezes during the measurement and the phases can not be heard clearly, abort the measurement, wait 30 seconds and re-measure blood pressure.

Remove the stethoscope ear pieces. Disconnect the cuff and record the BP reading and the zero reading. **DO NOT SUBTRACT THE ZERO READING UNTIL BOTH MEASUREMENTS ARE COMPLETED.**

Measurement #2

After waiting 30 seconds with the participant's arm passively elevated for 5 seconds and on the table for 25 seconds, repeat as in measurement #1. After both readings are completed, the bellows control valve should be left in the OPEN position. If four identical consecutive zero read-

ings are obtained, the maximum and minimum zeros should be checked before the device is used with another participant. If the maximum and minimum are confirmed, the device should be sent out for service.

When finished recording the two RZ BP measurements, subtract the zero value from the reading to get the actual (corrected) systolic and diastolic values. Because of the importance of BP data in PREMIER, all arithmetic must be done with a calculator after two readings have been completed.

If unable to hear, discontinue the measurement and wait 30 seconds. Then inflate the cuff to the maximum inflation level. Leaving the cuff inflated, have the participant rapidly open and close his or her fist six to eight times, and then proceed with the measurement.

Missing BP Information

If for any reason the technician is unable, or has forgotten, to complete any portion of this protocol and the participant has left this area, draw two horizontal lines through the relevant spaces on the data collection form. This is the correct way to indicate the missed information. If an entire reading is missed or is technically invalid and the participant is still in the clinic, a replacement reading should be obtained. Be sure to completely deflate the cuff and start over with a complete replacement reading. **Under NO other circumstances, however, may a replacement reading be obtained simply because the results seem unusual.** Always wait at least 30 seconds between readings.

Changing the Peak Inflation Level

Occasionally, the Korotkoff sounds may be heard as soon as one places the stethoscope over the brachial pulse. If this happens, the peak inflation level used was too low. Immediately deflate the cuff by releasing the thumbscrew and disconnecting the cuff tube. The participant should then hold the cuff-wrapped arm above the head level for five seconds. Draw a line through the previously recorded pulse obliteration pressure and peak inflation level. Increase each number by 10 and write the new number above the original one, as shown below.

	130
Pulse Obliteration Pressure	~~120~~
	+60
	190
RZ Peak Inflation Level	~~180~~

Proceed with BP measurement, starting at the new peak inflation level.

Overview of Training and Certification

Personnel

All persons obtaining PREMIER RZ blood pressure measurements are required to undergo training and certification in RZ BP measurement technique by a certified trainer. Each clinical site designates two site-specific trainers, one of whom must be trained and re-certified by the study-wide trainers. Each site will also designate an unlimited number of technicians, who must be trained and certified by either the site-specific trainers or the study-wide trainers.

Training and Certification

Study-wide trainers train and certify the site-specific trainers, who in turn train the technicians and another trainer at their sites. The Coordinating Center, on receipt of all necessary documentation of successful training, certifies all technicians. At least one trainer from each site is recertified by the study-wide trainers. These trainers then recertify the technicians and (if necessary) the other trainer at their sites. All BP staff, including trainers and technicians, are recertified between cohorts (approximately every six months). All study-wide master trainers are recertified centrally every 6 months. Certification is verified by the Coordinating Center.

Introduction

In order to standardize the previously described methods of blood pressure measurement and to ensure that a high level of performance is attained a two-stage training program has been developed. Before the actual initiation of standardized measurements, a program of training and certification must be provided so that all staff responsible for recording blood pressure readings will be certified as having met a stipulated level of performance. At least one coordinator will be recertified centrally for blood pressures at an annual training session.

The training strategy adopted by PREMIER is a two-stage blood pressure program. Before the program begins, each clinical center will identify two specific trainers for that clinic. One trainer from each clinical center will meet centrally in June 1999 for the first stage of training. The full training program will be presented at this time. The trainers who pass the program will be certified as Blood Pressure Trainers. The trainers can, in turn, train additional technicians in the clinical centers and another designated trainer. This is the second stage of training. To this end, each center will be provided with the full set of training materials needed to reproduce the same program for their field and clinic staff. In this second stage, the Coordinating Center will receive documentation of each technician's training performance from the trainers in the clinical centers (including the successful completion of the written test [Form #303] and the Blood Pressure Certification Form [Form #304]). The sites will enter the technician's answers to the video exam (Form #319) into the BP certification module in the data entry/management application. The video test will immediately be scored and if the technician passed the exam, the rest of their

certification results can be entered. If the technician does not pass the video test, they must re-take the test until they pass. After completion of data entry of the certification forms, the original exams should be copied and sent to the Coordinating Center for QC checks (attn:Mike Allison). Various reports are available in the certification system. These reports can be generated at any time to identify who needs to be re-certified and when (see the Certification User's Manual for more details).

Through this scheme, training will be the responsibility of both the clinical centers and the Coordinating Center. The CC will, in addition, remain responsible for overall monitoring and quality control.

Staff will be recertified according to the following schedule:

- All blood pressure master trainers are re-certified centrally every 6 months
- All blood pressure trainers will recertified every 6 months during the face-to-face Steering Committee or at a special training site.
- All blood pressure technicians are recertified by their local trainers during the breaks between cohorts (approximately every six months).
- All blood pressure technicians are required to meet these recertification deadlines unless they have been specially certified (e.g., new hires) during the three months prior to the start of the recertification window. If they have been certified for less than three months prior to this time they may wait for the following certification window before being recertified.

Steps Needed for Certification and Recertification

- First Step

Before starting the certification/recertification process, technicians should read/review Chapter 17, pages 17-1 through 17-9, of the PREMIER Clinical MOP.

- Second Step

All staff taking PREMIER blood pressure outcome measurements must attend a PREMIER training session, or receive training from a certified PREMIER blood pressure trainer.

- Third Step

The third step is a series of blood pressure readings presented on a videotape to test the technician's identification of the systolic and diastolic Korotkoff sounds. The tape mimics the actual

blood pressure measurement setting by providing a series of blood pressure readings which consist of both the visible falling of the mercury in a sphygmomanometer and the audible Korotkoff sounds. A technician is certified if the criteria of the scoring procedure are successfully met. The criteria of the scoring procedure are not available to the clinical center or to the technicians. The scoring will occur after the entry of the technician's test sheets (Forms #303, 304, 305, 319) into the certification application (on the workstation) is complete. The certification application will alert the data entry technician if the BP technician does not pass the video test (see the Certification User's Manual for more details).

- *Instructions for Taking the Videotest*. Viewing of the videotape, "Measuring Blood Pressure," may be done in a group or individually. The videotape consists of one practice reading followed by twelve systolic and diastolic sequences. After each sequence, the technician should record, on the recording sheet provided (Form #319), the systolic and diastolic reading for that sequence. All entries should be complete, legible, and written in black ink. The manometer in the videotape is read exactly as one would read in actual practice. Each blood pressure should be read rounded up to the nearest even digit. Each BP reading should agree within ±4 mmHg on any reading (systolic or diastolic).

▸ Fourth Step

The fourth step of blood pressure certification is the completion of the Blood Pressure Written Examination (Form # 303) after lectures have been presented. This is a short examination consisting of questions that test the blood pressure technician's knowledge and understanding of the measurement technique detailed in the training course. Technicians must score 100% on this exam. Scoring of the exam should be completed by the master trainer.

▸ Fifth Step

The fifth step is the successful completion of Form #305. The trainer is to verify the correct procedure for blood pressure measurement by observing the technician in one or more complete and uninterrupted exercises of the full procedure (Form #305).

- *Y-Tube Stethoscope Observations.* Y-tube stethoscope observations are made for certification and recertification. The technician and trainer listen with the Y-tube and record the values on separate sheets (see Blood Pressure Certification Form #304). Two measurements on each of three subjects should be obtained. Readings by the trainer and technician should agree within ±4 mmHg on any reading (systolic or diastolic), and averages should agree within ±3 mmHg.

▸ Sixth Step

The sixth step is the successful completion of Form #304. The trainer is to verify the correct

procedure for blood pressure measurement by observing the technician in three y-tubed readings, with the trainer and technician simultaneously recording blood pressure on three different individuals (Form #304).

- *Observation of BP Measurement Procedures and Techniques*. All BP technicians must be checked to ensure that they are following procedures correctly and utilizing proper measurement techniques. This is necessary for both certification and re-certification. If these measurements are made on a study subject, the observed blood pressure measurements for training may not be used for data. The trainer uses the BP Observation Checklist (Form #305) to grade the technician while he or she follows the entire BP protocol to obtain two readings on a non-study or study individual, using a regular stethoscope. The trainer should be outside the immediate work area of the technician and should not make any comments during measurement. This part of the certification process should be done separately from the Y-tube certification. When carried out without procedural errors, this record (Form #304) should be completed, signed, and included with the certification packet for the technician. Errors of procedure should be reviewed, discussed, and corrected until one completed determination is accomplished without error.

After successfully completing the certification/re-certification, the completed forms are entered into the Certification System (see the Certification User's Manual for details). As a means of maintaining a high level of quality and standardization over time, blood pressure technicians will be re-certified between cohorts (approximately every six months). The Coordinating Center will notify the clinical centers as to the schedule and requirements of the re-certification. A further description is in the section called Annual Recertification and Retraining.

Summary of Requirements for Blood Pressure Certification and Recertification

<u>Certification</u>

1. Read Blood Pressure Assessment (Chapter 17, pg. 17-1 through 17-9 of the MOP).
2. Attend PREMIER training session, or receive training from a certified PREMIER blood pressure trainer.
3. Successfully complete all blood pressure examples on Videotape Test Sheet (Form #319) (100% correct).
4. Successfully complete the Blood Pressure Written Exam (Form #303) (100% correct).
5. Successfully complete blood pressure measurement technique and procedure. Record and submit results on Blood Pressure Observation Checklist Form (Form #305).
6. Successfully complete three Y-tube stethoscope readings (average of three readings <u>+</u>4 of trainer measurements), using three different people, with PREMIER BP Trainer. Record and submit results on the Blood Pressure Certification Form (Form #304).

Recertification

1. Required every six months for clinic staff and for Blood Pressure Trainers. At least one trainer at each site must be recertified centrally every six months.
2. Successfully complete blood pressure measurement technique and procedure. Record and submit results on Blood Pressure Observation Checklist Form (Form #305).
3 Successfully complete three Y-tube stethoscope and dual readings using three different subjects. Record and submit results on Blood Pressure Certification form (Form #304).
4. Successfully complete the Blood Pressure Written Exam (Form #303) on blood pressure measurement (100% correct).
5. Successfully complete all blood pressure examples on Videotape Test Sheet (Form #319) (100% correct).
6. Must be actively taking blood pressure measurements using a random zero sphygmomanometer (at least 4 measurements per month). More than one violation of this criteria in any consecutive three month interval results in a lapse of certification.

Study Forms Required for Certification Procedures

Four study forms are required for certification.

1. Blood Pressure Written Examination (Form #303) and its key.
2. PREMIER Blood Pressure Observation Checklist Form (Form #305).
3. PREMIER Blood Pressure Certification Form (Form #304).
4. The Videotape Test Sheet (Form #319).

These four forms may be found in the Quality Control section of the PREMIER Forms Manual.

Blood Pressure Measurement Quality Control

Overview

Two primary methods exist for monitoring the performance of trained technicians in the measurement of blood pressures during the course of a clinical trial. The first is the completion of a biannual recertification. The second is the regular monitoring by the Coordinating Center of all technicians for digit preference.

In addition to these, PREMIER has adopted and instituted a comprehensive program to insure the collection of high quality blood pressure measurements. Factors contributing to this include:

1. Recruitment of the most qualified personnel.
2. Standardized training and certification.
3. Retraining of technicians having difficulties with standardized measurements.

4. Observations once every three months by the Blood Pressure Trainer of BP measurement techniques of the blood pressure technicians on either a participant or nonparticipant, using the Quarterly Checklist for Monitoring Blood Pressure Observers (Form #302). One checklist is used for each blood pressure technician. These should be kept on file and will be reviewed at site visits.
5. Biannual (every six months) simultaneous Y-tube observations of each technician by the blood pressure Trainer on either a participant or nonparticipant (described in Bi-Annual Y-Tube Stethoscope Observations).
6. Frequent staff meetings to provide feedback.
7. Continuous editing and analysis of data by the Coordinating Center.
8. Presentation of data analysis to the clinical centers by the Coordinating Center to provide feedback three times per year.
9. Equipment maintenance program (described in Local Blood Pressure Equipment Maintenance and Mercury Toxicity Safety Responsibility).

Monitoring for Digit Preference

It is well documented in other large blood pressure studies that even well trained technicians have the capability to lapse into an unconscious digit preference over time. Digit preference is defined as a predilection to record the terminal digit of a blood pressure measurement as either a "0" or a "2" or a "4" or a "6" or an "8", rather than the actual value. For example, a technician with a "0" digit preference may record an 82 mmHg DPB (or a 78 mmHg) as 80 mmHg.

NO TECHNICIAN SHOULD EVER HAVE A DIGIT PREFERENCE.

The Coordinating Center will provide monthly reports on digit preference of certified blood pressure technicians. Because of the numbers of analyses, it is assumed that some of these reports will indicate "significant" digit preference by chance alone. Many others will serve as evidence of mild digit preference. Since there are five possible terminal digits for each blood pressure (0, 2, 4, 6, 8), the expectation of any large number of readings is that 20% of readings will end in each of those digits. For the purposes of responding to digit preference reports on individual technicians involving 30 or more blood pressure readings, the Coordinating Center will act as follows:

1. No statistically significant digit preference: report to centers; center will share individual data with each technician.

2. Statistically significant digit preference, but no terminal digits occurring less than 16% or greater than 29% of the time: report to centers; center will share individual data with technician and counsel to be careful about technique.

3. Statistically significant digit preference and one or more digits reported on 30-39% or 10-15% of readings: report to centers; center will share individual data and review technique

with technician.

- Statistically significant digit preference of this magnitude persists on next report: formal recertification must occur within one week of second report; observation and counseling should follow.
- Statistically significant digit preference absent on next report and observed distribution includes no digits >29% or <16%: return to usual monitoring schedule.
- Digit preference improved, but still statistically significant: review technique; monitor for continued digit preference; if significant on third consecutive report, regardless of range, recertification is required within one week of receipt of the third report. If more than one week elapses, the technician must cease taking blood pressure measurements until such time as he or she is recertified.

4. Statistically significant digit preference; one or more digits reported $\geq$40% and/or $\leq$10% of the time and/or odd numbered terminal digits reported: Coordinating Center will notify PI/project director and discuss case individually; recertification required as soon as possible, but in no case later than one week after notification.

In addition, the Coordinating Center will raise for discussion any situations that appear to be problematic for the trial. This might include individual technicians exhibiting extremes of digit preference or repeated, uncorrected levels of digit preference, or centers that collectively exhibit unusual levels of digit preference. The Steering Committee may take action specific to such cases at its discretion. Coordinating Center report on digit preference will not reveal the specific digit that is biased.

In addition to the monthly digit preference reports, the CC will periodically issue additional blood pressure QC reports for review by the measurement and quality control committee. These will include, for example, reports on the variation in readings during a given test session. The measurement committee will develop appropriate action levels after review of these reports.

Responsibilities of the Coordinating Center and the BP Trainers

It is the responsibility of the Coordinating Center to centrally train and certify the BP Trainers. While it is primarily the responsibility of the trainers to return to the clinical centers and train other technicians, these technicians must still be certified by the Coordinating Center before being allowed to take official study measurements.

Each site is required to have at least two certified trainers. If, between recertifications, the Coordinating Center and/or a trainer has evidence that a problem may exist with a technician, the three parties will discuss the matter. It may be necessary for the Coordinating Center to temporarily rescind a certification and for the clinical center to retrain the technician. In this case, until the technician is recertified, he or she may not take blood pressure measurements.

It is also the responsibility of the Coordinating Center to monitor the specific activities of the BP trainers. In addition to the continuous monitoring of all incoming blood pressure data (e.g., for digit preference or bad values), the files of the biannual blood pressure checklists and maintenance logs (Forms #302, 306, 307, 320) will be reviewed at each site visit for completeness and accuracy. Finally, the master trainers are recertified centrally twice each year. If a technician takes fewer than four readings in any three month interval, she must be observed by a blood pressure master trainer, and Form #305 must be completed. The Coordinating Center will notify sites and follow up to make sure the observation was completed. Once participant screening is completed, unblinded master trainers will recertify quarterly using the Y-tubing process (Form #304), since they will not be able to take follow-up blood pressure measurements on participants. Two of these quarterly certifications occur at the central training, and two are done locally.

Maintenance of Random-Zero and Conventional Sphygmomanometers

Introduction

Each clinical center is responsible for the proper operation and maintenance of its BP equipment. Responsibility for proper maintenance is assumed by the clinic coordinator or designated person, and all staff are instructed to report promptly any real or suspected equipment problems to that person. All checks, inspections, and cleanings are documented and recorded by date in a permanent log maintained separately for each unit. All maintenance logs and biannual checklists (Forms #306, #307) should be stored in the permanent log binder. Problems and solutions are also recorded there. Logs will be reviewed by CC staff at periodic site visits and the CC will periodically make requests for copies of these documents for quality control checks.

The standard and RZ manometers should be checked during each use for problems in the following areas:

1. The zero level of the standard manometer
2. Mercury leakage
3. Dirt or mercury oxide deposit in the manometer column
4. The condition of all tubing and fittings

The standard and RZ manometers and cuffs should have a quarterly inspection on the following:

1. Valves and tubing of cuffs should be in good workable order
2. Should be free of dirt or mercury oxide deposit in the manometer columns
3. No mercury leakage
4. Tubing and fittings on both should be tight and free of leaks
5. Bellows valve on RZ should be free moving

The Standard and RZ manometer and cuffs should be thoroughly inspected and cleaned (if

necessary) biannually. The inspection should include the following:

1. Y tubing of RZ and Standard to check comparison
2. Screw cap should be tight
3. Valves of cuffs should be moving freely
4. Both the min and max zero levels should be checked
5. Both machines should be level on the stand
6. Bellows valve on RZ should be free moving
7. Dirt or mercury oxide deposits in the manometer columns should be cleaned
8. No visible Mercury leaks
9. Tubing and fittings should be tight and free of holes or leaks

The equipment should be cleaned if inspection indicates that cleaning is necessary, or at least once per year. In addition, every three months the accuracy of the RZ device should be checked using a standard manometer and a Y-tube and RZ zero levels should be checked. All sphygmomanometers used in PREMIER should be sent in for an overhaul prior to screening if they have not been used on a regular basis in the past year or if they have not been overhauled in the past 5 years text .

Anaeroid sphygmomanometers (if used for home visits) should also be inspected quarterly and cleaned once per year, or more often as needed. Anaeroid sphygmomanometers should be checked for accuracy every three months while in use by Y-tubing with a correctly functioning standard sphygmomanometer.

Equipment Maintenance and Safety

The condition of the instruments for blood pressure measurement is too often ignored in common practice and should be a special responsibility of the trainer or other designated staff member. This person **should be acquainted with mercury toxicity safety procedures** as well as construction and function of all the blood pressure equipment. The cleanliness and general working order of the cuffs and stethoscopes can usually be determined by simple inspection. For both the conventional and random-zero (RZ) type manometers, however, proper handling of breakable parts and of mercury and oxidized waste requires more careful attention. Guidelines for maintenance of the manometers are outlined here in some detail.

General Guidelines

1. The objective of maintenance of all sphygmomanometers is to ensure their accuracy for blood pressure measurement. The manometer column must be clean and the system free of mercury leakage. The zero level for the conventional device should be accurately read as 0 mmHg at the top of the mercury meniscus. The “zero” levels for the random-zero (RZ) device should have a range of approximately 20 mmHg between the maximum and the minimum “zero” level. These values should remain constant for a given instrument, and the maximum “zero” for each instrument should

be indicated by a label on the front of the machine itself, for comparison to zero levels obtained during actual readings taken with the device.

2. These devices should be cleaned and checked thoroughly on a quarterly basis or approximately every three months. Quarterly inspections should ensure there has been no mercury spillage or leakage and no obvious malfunction of the device. These inspections should include checks for: mercury leakage, operation of valves, manometer columns for dirt or mercury oxide deposit, and condition of all tubing and fittings.
3. Procedures for inspecting the RZ Manometer (RZM) are outlined below. The manometer portions of both instruments are produced by W. A. Baum Company (Copiague, New York 11726), so that maintenance for this portion of the two devices is the same, as is the case for cuffs, bulbs, and air control valves. More detailed instructions covering these parts are provided in the Baumanometer Service Manual, which is available from the W. A. Baum Company.
4. **Work area and mercury spillage.** All blood pressure devices used in PREMIER contain mercury, which is a volatile metal at room temperature. In view of the problem of spillage and retrieval of this material, a definite work area should be designated for all manipulations. This area should be in a well-ventilated room. Rugs should not be present. The work bench should be a flat, smooth surface which can be easily cleaned, with adequate space. All work should be done in a large tray or basin with edges that will contain any mercury spill that may inadvertently occur in the process of maintaining the machines. A mercury cleaning solution which inactivates elemental mercury and prevents it from vaporizing should be kept in stock in the work area and the person doing the work should wear gloves and a lab coat with no pockets and should remove rings, watches or other metallic objects from his/her hands. A procedure should also be developed for proper handling of accidental mercury spills and all staff made aware of the procedure. Institutional safety regulations at each site should be reviewed and followed.

Common Problems with—and Solution for—both Manometers

Dirty manometer column

- This is due to dirty or oxidized mercury and is usually evident near the zero. Oxide and dirt near RZM "zero" can result in too high "zero" readings because mercury hangs on the column wall above its equilibrium level. This does not affect conventional manometer readings, but it is hard to see the meniscus and hence to check actual zero.
- Remove the glass manometer column. See Baum instructions for removal of column from conventional manometer.
- Clean the glass column from its top towards its zero, with the "super" pipe cleaners available from Baum. Hold the column over a container to catch mercury as the cleaner is pushing through, and brush the soiled end of the cleaner into the container.

Mercury leakage

This can be due to any of the following:

- loose or leaky screw cap at top of manometer
- manometer column cracked, chipped, or improperly seated
- leaky manometer column gaskets
- tilting RZM with mercury reservoir valve open
- loose or leaky RZM bellows air bleed screw cap

The mercury level will not remain constant when the bulb valve is closed.

- Connect the manometer to a cuff which is around a one pound coffee can. Pump up the cuff and begin to pinch the tubing closed, starting at the manometer tubing.
- By a process of pinching the tubing at 1-2 inch intervals up to the cuff and then down to the bulb, you will locate an air leak.
- If an air leak is found to be in the cuff bladder or the tubing other than the connections, the bladder may need to be replaced.
- If the air leak is found in the connections or in the bulb valve, a little silicone spray may alleviate the problem.

Inspection of the Random-Zero Manometer

Unless obviously damaged due to dropping or other accident, the RZM is expected to operate without disturbance of its measurement performance. Quarterly checking should be done, however, to ensure against undetectable internal leakage, or malfunction of the "randomizing" mechanism.

1. Place device in usual operating position, with reservoir valve open (to side).

2. Remove mounting screws from the front and rear of the wooden casing and remove the casing, keeping the instrument upright at all times.

3. Inspect the base and moving parts for any evidence of mercury leakage.

4. Bleed the air out of the R-Z system and check for mercury leaks.

Using a 30 ml or larger syringe and a length of tubing, apply greater than 200 mmHg pressure to the mercury column. (A syringe gives faster and better control than a cuff and a bulb for this purpose, but the technician must be careful not to pull negative pressure.) If a cuff is used, it can be wrapped around a one pound coffee can. Watch the rise of mercury in the chamber, and maintain or increase the pressure until the mercury rise into the narrow vertical stem at the top of the chamber. If mercury does not enter the stem despite prolonged high pressure, deflate the cuff and repeat, after slightly opening the thumbscrew at the top of the stem. This will permit escape of any trapped air. When the mercury has entered the stem, close the thumbscrew firmly (but not

excessively tight) and deflate the cuff.

5. Verify the maximum "zero" obtainable

- The bellows valve should be in the "OPEN" position, and no pressure should be in the cuff. The cam should rotate freely.
- Set the cam manually in such a position that the level on the end of the cam will contact the moving wall of the chamber after the shortest possible displacement of this wall toward the cam. (This position draws the least mercury into the reservoir and produces the highest "zero" level for the amount of mercury in the device at this time.)
- Inflate the cuff above 200 mmHg and maintain it at this pressure until the chamber wall has come to rest against the bevel of the cam.
- Turn the valve to "CLOSE," wait a full five seconds, and deflate and disconnect the cuff.
- Record the zero level. It should match the maximum value on the label that was placed on the face of the manometer by the trainer. If it does not, a new label should be created at the site by the person responsible for RZ maintenance.

6. Verify the minimum "zero" obtainable

- Repeat exactly as for (5) above, except set the cam so that the moving wall of the reservoir will move its maximum distance before contacting the cam. (This position draws the most mercury into the reservoir and produce the lowest "zero" level for the amount of mercury in the device at this time.)
- Ensure that full pressure in the cuff is maintained until the wall of the chamber comes to rest against the bevel of the cam; this may take several seconds.
- Turn the bellows valves to "CLOSE," and deflate and disconnect the cuff.
- Record this zero level. It should match the minimum value on the label that was placed on the face of the manometer by the trainer.

7. Adjust zero levels if needed

There should be a 20 mm difference between the maximum and minimum values. Changes of zero levels are due either to loss of mercury or to air leakage at the bellows air bleed screw; accuracy of readings is not affected. To adjust zero levels, however, mercury must be added or removed from the system. If the minimum or maximum zero levels consistently exceed the determined levels, or any other peculiar problems are noted, notify the Coordinating Center.

CAUTION: Mercury vapor is very toxic: Tiny droplets vaporize more rapidly than bulk. All loose mercury must be collected and inactivated. One effective and convenient product for

mercury vapor reduction is HgX, a powder produced by Acton Associates, 1180 Raymond Boulevard, Newark, NJ 07102. It is recommended that all work be done in a container, such as a plastic dish pan, when mercury is to be transferred, that gloves and lab coat be worn, and that the area is well ventilated.

If the minimum zero level is below 0:

- Open the bellows control valve and the valve at the top of the mercury reservoir, unscrew and remove the knurled cap at the top of the manometer column, and remove the air bleed screw at the top of the bellows chamber.
- Pour clean mercury into the top of the manometer tube, using a hypodermic syringe barrel or tight paper cone as a funnel. (As Baum writes, mercury can be cleaned of floating dirt and oxides by pouring it through a rolled cone of ordinary scratch paper with a pinhole at its apex. Note that some mercury will stick on and in the paper, so handle with care, and dispose of the paper properly). About 400 grams (or 14 ounces) of mercury are needed to fill an instrument for a zero range of near 10 to 30 mm.
- Firmly screw the knurled cap onto the top of the manometer column, and apply pressure to the mercury reservoir until the mercury rises into the vertical air column at the top of the bellows chamber. Tighten the air bleed screw quickly and firmly, while the mercury is a short distance into the vertical air column.
- Apply enough additional pressure to raise the mercury to near the top of the manometer column (if it is not already that high); then release the pressure, thus to collect mercury droplets and clear the column of air bubbles. There are likely to be air bubbles trapped on the walls of the plastic tube at the bottom rear; these can sometimes be removed by tapping the tube sharply, but they are, at any rate, of no consequence.
- Determine zero range and adjust as needed.

If the minimum zero level is greater than 4, or the maximum is greater than 24:

- Unscrew and remove the knurled cap from the top of the manometer column. Using a syringe with a small tube, such as a catheter, remove the mercury from the manometer.

8. <u>Check whether the spin wheel and cam spin freely.</u>

- Turn the bellows valve on the front of the manometer to “OPEN” and allow the wall of the chamber to move back to its resting position.
- Spin several times the rubber-rimmed wheel used in setting the “zero” level for each reading. Note whether the cam spins freely, and whether it is excessively loose.
- Adjust the spin by slightly loosening or tightening the mounting screw at the end of the cam.
- After any such adjustment, recheck the spinning wheel repeatedly to ensure against tightness or looseness of the cam.

If spin wheel and cam are stuck (with bellows control cock open and all pressure released) or the rise of the mercury column is jerky as pressure is raised, there is usually binding or friction between the bellows plate center boss and the centering pin. Accuracy of readings has not been affected. A drop of good, light machine oil takes care of most such problems.

9. To remove the manometer column for cleaning or for inspection of it and of gaskets:

    - Set the cylindrical cam for maximum bellows volume, and open the bellows control valve.
    - Raise the reservoir pressure to about 280.
    - Close the bellows valve and release pressure on the reservoir.
    - Tilt the RZM to the right (reservoir on down side) until all mercury has disappeared below the manometer column. Close the reservoir valve (handle to front). Rest the RZM on its right side, with the spin wheel above the table surface.
    - The manometer column may now be removed.

10. Maintenance requirements are minimal, but essential.

    - A very occasional drop of light machine oil is recommended on moving parts, including the bellows plate centering pin.
    - Do not, however, oil the bellows control valve stem or the mercury reservoir valve.
    - Ensure that moving parts are free without too much slack.

For BP Trainers Use Only

Procedures for Training and Certifying BP Technicians—<u>For Trainers' Use Only</u>

Before presenting information the trainers should read the section on Preparation for Trainers. Lectures 1-4 (two with slides) are offered in this section to acquaint the technician with the subject of blood pressure and its measurement. The training of potential blood pressure technicians should begin with a general discussion of blood pressures and some of the history of blood pressure measurement. The first lecture, "Blood Pressure Measurements—Problems and Solutions," addresses three topics and also reviews some of the problems and solutions in blood pressure measurement. This presentation is quite limited with respect to the physiology of blood pressure regulation and the hemodynamics leading to production of the Korotkoff sounds. The objective instead is to provide sufficient information for <u>any</u> technician of high school graduate level or beyond, without prior clinical training, to appreciate the significance of the auscultatory signals for blood pressure reading and to recognize those factors of greatest importance for the quality of the readings.

The second lecture, "The Random-Zero Device," is accompanied by a slide series that aids in the explanation of the mechanics and the proper use of this device.

The third lecture, also accompanied by slides, is entitled, "Procedures in Blood Pressure Recording." This presentation gives instructions in the blood pressure measurement technique adopted by HDFP, TOHP, DASH, and DASH2. Procedures for using both the conventional and the random-zero devices are given.

The fourth lecture "Equipment Maintenance and Mercury Toxicity Safety" gives guidelines for maintenance procedures.

Trainers in the Clinical Center

There are three distinct sections involved in the responsibility of the local trainers. First is the preparation for the training session. Second is the time scheduling of the sessions. And third is the documentation of certification to the Coordinating Center.

Preparation for Trainers

Gather all the blood pressure equipment:

- Both the conventional and random-zero manometers
- All four basic sizes of blood pressure cuffs with bulbs
- A bell stethoscope

Familiarize yourself with all the blood pressure equipment. Prepare for mercury safety procedures and prepare an equipment maintenance schedule. Check all random-zero sphygmomanometers for maximum and minimum zero levels. The standard sphygmomanometers should be

checked so that the top of the mercury meniscus is at the zero marking. The stethoscopes should be clean and turned to the bell. The cuffs and air valve should be checked for air leaks.

Gather all the Training Materials

- This training manual
- Blood Pressure Written Exam and answer key (Form #303)
- Blood Pressure Certification Form (Form #304)
- Blood Pressure Observation Checklist (Form #305)
- Videotape Exam (Form #319)
- 2x2 slide projector and carousel
- Videotape machine
- Black ball-point pen
- Slides and videotape

You should carefully familiarize yourself with all the training materials. Only you know how much practice will be needed for you to present the lectures to your technicians. Be sure you have plenty of photocopies of all the forms (the Written Examination [Form #51], Blood Pressure Certification Form [Form #52], and the Videotape Test Sheet [Form #58]). Familiarize yourself with the operation of the slide projector and videotape machine.

Training Tips

- Schedule the training sessions over a period of days. An unhurried schedule gives the technician a chance to absorb and demonstrate the procedures and knowledge with more confidence. Remember, you may be training someone who needs to unlearn previously learned blood pressure procedures. Also remember the stethoscope can cause ear discomfort when used for several hours at one time.
- Try to keep the group size workable. The lectures may work for a large group, but consider the waiting/noise factor when scheduling the written test, blood pressure practice/evaluation, and the videotape viewing.
- The certification of the technician and duties as a technician should not be planned for the same day. The technician cannot complete the certification and begin taking participant blood pressures that same day. Plan time to allow for entry of the written exam (Form #303), the video exam (Form #319) into the data entry/management application, and generation of the notice of certification from the application.

Documentation of Certification

- Each person in the clinical center that will be filling out any part of a blood pressure form will need a staff ID code. This includes the blood pressure technicians. Only one code number should ever be assigned to one person, no matter how many changes in status might occur.

- The Written Examination (Form #303) should be taken by the technician and graded by the trainer. If there are any differences in responses, it should be discussed and clarified. The trainer should indicate those responses that were discussed by initializing them.
- The Blood Pressure Certification Form (Form #304) should be carefully followed to ascertain that the technician has a clear understanding of the procedures. This evaluation should be completed by the trainer as a passive observer. Avoid prompting the technician. The technician should complete one or more complete and uninterrupted exercises of the full procedure. Errors of procedure should be reviewed, discussed, and corrected. When carried out without procedural errors, this record should be completed, signed, and included with the certification packet of the technician.
- When the videotape test (Form #319) is taken, remind the technician to insert leading zeros where necessary and to complete the entire form. The test will be graded upon entry into the data entry/management application on the PREMIER file server. If a systematic problem is discovered via computer scoring, the Coordinating Center will instruct you as to the type of problem discovered. The specific problem would not be identified to the technician, as this may artificially bias the technician's responses. Retraining, possibly by Y-tube readings, may help to identify and correct the problem. If the problem is not corrected within several retrainings, the problem is probably auditory and technician would need to be hearing tested and, if correction is not possible, excluded from taking blood pressures. If a hearing correction is possible, the technician will need to be retested. The Coordinating Center needs to have complete documentation of the certification. We suggest the trainer keep the originals and send photocopies to the Coordinating Center. The Coordinating Center will instruct the trainer when recertification should be scheduled, on a biannual basis.

Lecture #1—Blood Pressure Measurement—Problems and Solutions

What is blood pressure? This question can be answered in many ways—for example, in terms of physiologic and sometimes pathologic processes which contribute to blood pressure regulation. Or, blood pressure can be described in terms of the striking excess in risk of death and disease which accompany high blood pressure levels. For our immediate purposes a more useful and more appropriate answer is, simply: Blood pressure is what is recorded when the measurement methods learned through this training program are carried out.

If we are defining blood pressure in terms of the means of measuring it, the nature of this measurement must be understood. A brief historical sketch is helpful. Measurement of blood pressure by means of the usual mercury manometer, cuff, and stethoscope is a method less than 100 years old, although Hales described experimental direct arterial pressure measurements over 200 years ago and Harvey described the circulation of the blood more than 300 years ago.

The start of this century was the period when current, indirect methods were introduced. These were more practical than the lethal method of Hales and qualify as what we would term today a

"non-invasive" technique. This indirect method, now almost universally employed, combines the work of Riva-Rocci, an Italian physician who developed the inflatable cuff, and Korotkoff, the Russian physician who described his auscultatory findings, heard through a stethoscope placed over the brachial artery, as an improvement over mere palpation of the radial pulse, a technique limited to detecting systolic pressure alone.

The report of Korotkoff's first observation is an informative summary of the specific sounds he described: "On the basis of his observation, the speaker has come to the conclusion that the completely compressed artery under normal circumstances does not produce any sounds. Utilizing this phenomenon, he proposes the auditory method of determining the blood pressure in man. The cuff of Riva-Rocci is placed on the middle third of the upper arm, the pressure within the cuff is quickly raised up to the complete cessation of circulation below the cuff. Then, letting the mercury of the manometer fall, one listens to the artery just below the cuff with a children's stethoscope. At first, no sounds are heard. With the falling of the mercury in the manometer, done to a certain height, the first short tones appear; their appearance indicates the passage of part of the pulse wave under the cuff. It follows that the manometer figure at which the first tone appears corresponds to the maximal pressure. With the further fall of the mercury in the manometer, the systolic compression murmurs are heard, which fade again into tones (second). Finally, all sounds disappear. The time of the cessation of sounds indicates the free passage of the pulse wave; in other words, at the moment of the disappearance of the sounds, the minimal blood pressure within the artery preponderates over the pressure in the cuff. Consequently, the manometric figures at this time correspond to the minimal blood pressure. Experiments on animals gave confirmative results. The first sound tones appear (10 to 12 mm) earlier than the pulse, for the palpation of which (e.g., in the radial artery) the inrush of the greater part of the pulse wave is required." [Quoted from Ruskin, A. *Classics in Arterial Hypertension*, Charles C. Thomas, Springfield, 1956 (pp. 127-128)].

With further refinement in criteria by which changes in sound quality are to be judged, we arrive very nearly, but not quite, at the level of technological advance applicable to the conventional mercury sphygmomanometer today. In summary then, we may define blood pressure as the phenomenon measured when the cuff, mercury manometer, and stethoscope are used in the standard manner by a trained technician to assess the cardiovascular status of a subject.

Discussion of blood pressure in these terms would be seriously incomplete, however, if we did not take account of the fact that important problems of measurement exist. It is imperative that these problems be recognized and, as far as possible, overcome. What are they?

An excellent review by Evans and Rose (7) distinguishes, first, random variation within each subject, and, second, systematic variation which they subclassify as follows: "(i) alarmingly large differences in estimation between technicians, sometimes as large as 15 mmHg..., (ii) effects of the circumstances of measurement, both emotional and physical (especially recent physical activity or change of position), (iii) seasonal changes, and (iv) relatively small errors due to overestimation of pressures in fat arms ...."

If these are the major categories of problems, what can be done to deal with them? With respect to random individual variation for each person, we obtain multiple readings on each occasion of observation and use as our estimate of blood pressure an average of two readings, always excluding the first inflation of the cuff (used only to estimate the peak inflation level).

What about the systematic biases? Taking those listed in reverse order, we may say the following. The fat arm should be wrapped in a cuff of appropriate size—to exclude the effect of a single cuff size in giving falsely high readings for participants with excessive arm girth. Effects of circumstances, especially activity and posture, can be dealt with by requiring that all reading be taken in the sitting position, only after a minimum period of five minutes seated at rest, according to carefully prescribed procedures. As to differences between technicians, a systematic difference as large as 15 mmHg would indeed be alarming, and in fact, unacceptable. In still another publication dealing with measurement of blood pressure, Rose presented in greater detail some components of the remaining technician differences in blood pressure readings. These components are considered as of two types, one type affecting chiefly the mean of a series of measurements, the other type chiefly distorting the reported frequency distribution of readings. This latter type includes terminal digit preference, which is the unconscious tendency to choose one digit over others in assigning the value of a reading and the prejudice against certain values. Factors affecting mean differences between technicians include mental concentration or reaction time, hearing acuity, confusion of auditory or visual cues, interpretation of sounds, rates of inflation and deflation of the cuff, and reading of the moving column of mercury.

Are there answers to these problems? Regarding hearing acuity, deficiencies can be excluded by satisfactory performance on the videotape test. Regarding the effects of prejudicial reading, a device can be used that is designed primarily to overcome this tendency, the random-zero device. For all the remaining problems, we have a single answer: TRAINING. We will talk shortly about the random-zero device and about the standard procedures to control the circumstances of measurement. Training will occupy the rest of our attention to blood pressure measurement, for a good number of hours. The method of training and its specific objectives are, therefore, worth brief discussion now.

Training in blood pressure measurement will take three forms. First, there will be lecture and slide presentations to acquaint you with the proper procedures for measuring blood pressure and also to familiarize you with the random-zero device. Second, you will be observed taking actual live blood pressure readings with a Y-tube stethoscope. The objective of live reading practice is to become thoroughly familiar with the details of standard procedure so that their performance becomes a matter of habit. Proficiency in this aspect of training will be assessed under observation by the trainer. And third, your ability to measure blood pressure accurately as a result of this training will be tested using a videotape to simulate the fall of mercury with accompanying Korotkoff sounds during an actual blood pressure measurement. You will be required to determine the systolic and diastolic levels for each subject in the film, within predetermined limits.

Our responsibility, in supervision of this training program, is to offer all possible assistance to each of you, individually, in meeting these requirements and in completing each step necessary for your certification as a qualified blood pressure technician. We trust that you will take every opportunity to raise questions and indicate to us any problems you may have in working with these materials and completing the program satisfactorily. Accurate blood pressure measurement is critical, and there are methods available to substantially reduce the systematic errors that we have recognized. Your participation in this program will take advantage of these methods to assure a highly qualified group of technicians.

Lecture #2—The Random-Zero Device

The random-zero device is essentially a mercury sphygmomanometer like the conventional device in common use. It differs in the important aspect that a mechanical addition allows the mercury level in the column to be varied for each reading and concealed from the technician until the systolic and diastolic readings have been completed. This arrangement thus avoids the technician bias which is often at play when the technician knows the actual pressure level as the reading is carried out.

How this device is operated and how its mechanical features fulfill the objectives of its design can best be appreciated by inspecting the device, by practicing its use, and by preliminary inside view. We will take this preliminary view first, through a series of slides, and later practice with it. Copies of the slides are maintained at the Baltimore clinical center (copies will be distributed to all sites and to the Coordinating Center). Listed below is the script to accompany each slide.

Slide# Script for Slide

1. As we have already discussed, the random-zero device and the conventional mercury sphygmomanometer are essentially very similar. This can be seen in comparing the two devices side by side. The random-zero device is unique, however, as the following slides will show.
2. The crucial distinction is the wheel on the righthand side of the random-zero casing. To get a little closer to the workings of the device, we may remove the front of the casing.
3. The manometer column, the cuff and its connections, and one notable feature: a lever controlling the reservoir outlet. This lever is always closed (i.e., turned to the left) for carrying the device and opened (i.e., turned to the right) for operating it. You might notice also that the mercury rests at a level well above 0 mm, even though the cuff is not inflated. Let's take a close look at the mechanism, that accomplishes this to see how simple it really is.
4. To remove the rear portion of the casing (which should be done only by the trainer or other authorized staff member, and only when necessary for adjustment or standardization) one needs only to remove two screws from the upper face of the device and two from the lower rear.

5. Now we can get a better look at the inside. You will notice right away that the wheel you spin from outside is larger in diameter than you might have guessed, and it occupies a central position in the internal mechanism of the device. The movable rear wall of the chamber is the large round disk up above, which is ringed with its rubber seal.
6. From directly behind you can seen the wheel in relation to the chamber wall, and also the black rubber air hose connecting the cuff with the top of the mercury-filled plastic hose which connects the bottom of the reservoir with the chamber.
7. In this view you can see the control knob which the technician operates to open and close the connection between chamber and reservoir. Also, nearly the whole movable chamber wall can be seen. What gets in the way is a long aluminum cylinder cam which we will want to focus on in a moment. From the side we can see the three key elements that give this device its special value: the rubber-edged wheel which is spun (from the outside) before each reading; the cylindrical aluminum cam which contains the rubber rim of the wheel and spins at the same time (and its beveled forward end which extends forward in varying degrees depending on where it comes to rest); and finally the movable rear wall of the chamber, which will be arrested in its backward movement when pressure is applied as soon as it contacts the cam. When the cuff is inflated, pressure on the reservoir will force mercury into the chamber until the wall reaches the cam and stops. The amount of mercury in the chamber at this point will determine the "zero" reading for this one time, aiding the technician to make objective readings unaffected by the knowledge of the true reading.

Lecture #3—Procedures in Blood Pressure Recording

These procedures in blood pressure recording were developed after extensive consideration and discussion of numerous approaches to measurement techniques. In addition to the selection of instruments and specification criteria for measurement, we specify methods for the entire sequence of steps in blood pressure recording. For all technicians, whether inexperienced in blood pressure measurement or accustomed to different procedures, it will be important to become intimately familiar with these procedures and to carry them out, as early as possible, as a matter of habit. As an introduction, the following series of slides is presented to demonstrate the steps involved for the recording of blood pressure. The sequence presented here illustrates use of both the random-zero and the conventional sphygmomanometers. Copies of the slides are maintained at the Baltimore clinical center (copies will be distributed to all sites and to the Coordinating Center). Listed below is the script to accompany each slide.

Slide# Script for Slide

Equipment and Supplies (Slides 1-11)
Arm Measurement (Slides 12-21)
Preparation for Actual Readings (Sides 22-27)
Pulse (Slides 28-37)
First Blood Pressure Reading (Slides 38-49)

Between Readings (Slide 50)
Second and Third Blood Pressure Reading (Slides 51-53)

1. The equipment needed by each technician includes a random-zero sphygmomanometer in good condition, and
2. A conventional sphygmomanometer.
3. Access is needed to the full set of cuff sizes for this population. These are commonly referred to as the child (or pediatric) or small adult, adult (or regular), large, and thigh (or extra large) cuffs, respectively.
4. The inflation bulb should operate smoothly and should perhaps be individualized to each technician.
5. The stethoscope, in good condition, should be switched for use of the bell in listening to the Korotkoff sounds.
6. A watch with a sweep second hand or with a digital second display, or a stop watch, is needed for measurement of the pulse rate and for timing certain other steps until they become a matter of habit.
7. A measuring tape in metric units is required for determination of the correct cuff size for each participant.
8. A ball point pen should be used for all data recording, preferably with medium or larger point, and black ink.
9. Requirements for furniture are simple but must provide for a comfortable resting position of the arm with mid-cuff at heart level.
10. The appropriate study form must be in place before measurement begins.
11. Stand for RZ and standard monitor so equipment can be read at eye level.
12. The right arm should always be used for measurements unless there is a medical reason not to use the right arm.
13. Measurement of the arm is required for selection of the proper cuff. For this measurement, the arm should be bare.
14. The measurements are taken on the right arm, with the participant standing, holding the forearm horizontal.
15. Arm length is measured from the acromion or bony extremity of the shoulder girdle,
16. To the olecranon, or tip of the elbow.
17. The full arm length from acromion to olecranon is measured, and
18. The midpoint is marked on the dorsal surface of the arm.
19. With the participant's arm relaxed at the side, the arm circumference is measured by drawing

the tape snugly (without indenting the skin) around the arm at the level of the midpoint marking. Care must be taken to keep the tape horizontal.

20. The chart of arm circumference measurements and corresponding cuff sizes is consulted, and
21. The proper cuff size is checked. Indicate the cuff size on the form.
22. The participate should then be seated with the elbow and forearm resting comfortably on a table with the palm of the hand turned upward. The area to which the cuff must be applied must be bare. The bend of the elbow should be at heart level.
23. Legs should be uncrossed and feet comfortably flat on the floor.
24. The brachial artery is located by palpation and marked (just medial to and above the antecubital fossa).
25. As is the midpoint of the rubber bladder within the cuff. Often this point is marked on the cuff itself.
26. The cuff is then wrapped about the arm so that the midpoint of the bladder lies over the brachial artery, and the mid-height of the cuff is at heart level.
27. Allow a five minute wait before taking the BP. Conversation should be limited during this time. You should leave the room after a brief explanation.
28. After the period of 5 minutes at rest has been completed, the radial pulse is counted for a timed interval of exactly 30 seconds.
29. The 30-second count is recorded.
30. The standard mercury sphygmomanometer is then connected with the cuff.
31. The manometer is positioned so that the midpoint of the column is at the technician's eye level when in position to carry out the measurement of blood pressure.
32. The radial pulse is located, and palpated.
33. The cuff is inflated quickly to 80 mmHg.
34. Slowly inflate at 10 mmHg at a time until the radial pulse can no longer be felt.
35. The cuff is quickly and completely deflated.
36. Record the pulse obliteration pressure (POP).
37. Calculate and record the peak inflation level (pulse obliteration pressure + 60). The peak inflation level used for BP measurement must be >180 mmHg.
38. To perform the measurement of blood pressure itself, the brachial artery is again palpated. Note that the arm remains bare.
39. The wheel of the random-zero is gently spun with the valve in the OPEN position.
40. The stethoscope ear pieces are put in place with the ear pieces positioned forward.
41. The bell of the stethoscope is placed carefully and without excessive pressure over the

brachial artery, just between the elbow crease and lower edge of the cuff.

42. With the valve still in the OPEN position, the cuff is inflated quickly and smoothly to the peak inflation level or to 180 mmHg, whichever is higher. Hold the mercury at this pressure for five seconds.
43. The valve is then turned to the CLOSE position.
44. The cuff is then deflated very steadily at 2 mmHg per second,
45. To a level 10 mmHg lower than the level of the last Korotkoff sound heard.
46. The mercury level is now dropped quickly to the "zero" level for this reading.
47. The observed values for the SBP, DBP, and "zero" values are recorded.
48. Remove stethoscope ear pieces.
49. Disconnect the cuff and record the zero reading. DO NOT SUBTRACT THE ZERO READING UNTIL ALL THREE MEASUREMENTS ARE COMPLETED.
50. Have participant raise arm for five seconds, then rest arm on table for 25 seconds.
51. The second and third readings are carried out exactly as the first.
52. After finishing both RZ BP measurements subtract the zero value from the readings to get the actual systolic and diastolic values.
53. All arithmetic must be done with a calculator after both readings have been completed.

Lecture #4—Equipment Maintenance and Mercury Toxicity Safety

(This lecture is essentially a repeat of the material covered under pages 17-22).

The condition of the instruments for blood pressure measurement is too often ignored in common practice and should be a special responsibility of the trainer or other designated staff member. This person **should be acquainted with mercury toxicity safety procedures** as well as construction and function of all the blood pressure equipment. The cleanliness and general working order of the cuffs and stethoscopes can usually be determined by simple inspection. For both the conventional and random-zero (RZ) type manometers, however, proper handling of breakable parts and of mercury and oxidized waste requires more careful attention. Guidelines for maintenance of the manometers are outlined here in some detail.

General Guidelines

1. The objective of maintenance of all sphygmomanometers is to ensure their accuracy for blood pressure measurement. The manometer column must be clean and the system free of mercury leakage. The zero level for the conventional device should be accurately read as 0 mmHg at the top of the mercury meniscus. The "zero" levels for the random-zero (RZ) device should have a range of approximately 20 mmHg between the maximum and the minimum "zero"

level. These values should remain constant for a given instrument, and the maximum "zero" for each instrument should be indicated by a label on the front of the machine itself, for comparison to zero levels obtained during actual readings taken with the device.

2. These devices should be cleaned and checked thoroughly on a biannual basis or approximately every six months. More frequent inspections should be made to ensure there has been no mercury spillage or leakage and no obvious malfunction of the device. Instruments used in clinics should be inspected weekly. Those inspections should include a check of zero levels, mercury leakage, operation of valves, manometer columns for dirt or mercury oxide deposit, and condition of all tubing and fittings.
3. If your biannual check and bimonthly fall in the same month complete both maintenance logs.
4. Procedures for inspecting the RZ Manometer (RZM) are outlined below. The manometer portions of both instruments are produced by W. A. Baum Company (Copiague, New York 11726), so that maintenance for this portion of the two devices is the same, as is the case for cuffs, bulbs, and air control valves. More detailed instructions covering these parts are provided in the Baumanometer Service Manual, which is available from the W. A. Baum Company.
5. **Work area and mercury spillage.** All blood pressure devices used in PREMIER contain mercury, which is a volatile metal at room temperature. In view of the problem of spillage and retrieval of this material, a definite work area should be designated for all manipulations. This area should be in a well-ventilated room. Rugs should not be present. The work bench should be a flat, smooth surface which can be easily cleaned, with adequate space. All work should be done in a large tray or basin with edges that will contain any mercury spill that may inadvertently occur in the process of maintaining the machines. A mercury cleaning solution which inactivates elemental mercury and prevents it from vaporizing should be kept in stock in the work area and the person doing the work should wear a lab coat with no pockets and should remove rings, watches or other metallic objects from his/her hands. A procedure should also be developed for proper handling of accidental mercury spills and all staff made aware of the procedure. Institutional safety regulations at each site should be reviewed and followed.

Common Problems with—and Solution for—both Manometers

Dirty manometer column

- This is due to dirty or oxidized mercury and is usually evident near the zero. Oxide and dirt near RZM "zero" can result in too high "zero" readings because mercury hangs on the column wall above its equilibrium level. This does not affect conventional manometer readings, but it is hard to see the meniscus, and hence to check actual zero.
- Remove the glass manometer column. See Baum instructions for removal of column from conventional manometer.
- Clean the glass column from its top towards its zero, with the "super" pipe cleaners available from Baum. Hold the column over a container to catch mercury as the cleaner is pushing through, and brush the soiled end of the cleaner into the container.

Mercury leakage

This can be due to any of the following:

- loose or leaky screw cap at top of manometer
- manometer column cracked, chipped, or improperly seated
- leaky manometer column gaskets
- tilting RZM with mercury reservoir valve open
- loose or leaky RZM bellows air bleed screw cap

The mercury level will not remain constant when the bulb valve is closed.

- Connect the manometer to a cuff which is around a one pound coffee can. Pump up the cuff and begin to pinch the tubing closed, starting at the manometer tubing.
- By a process of pinching the tubing at 1-2 inch intervals up to the cuff and then down to the bulb, you will locate an air leak.
- If an air leak is found to be in the cuff bladder or the tubing other than the connections, the bladder may need to be replaced.
- If the air leak is found in the connections or in the bulb valve, a little silicone spray may alleviate the problem.

Inspection of the Random-Zero Manometer

Unless obviously damaged because of dropping or other accident, the RZM is expected to operate without disturbance of its measurement performance. Periodic checking should be done, however, to ensure against undetectable internal leakage, or malfunction of the "randomizing" mechanism.

1. Place device in usual operating position, with reservoir valve open (to side).

2. Remove mounting screws from the front and rear of the wooden casing and remove the casing, keeping the instrument upright at all times.

3. Inspect the base and moving parts for any evidence of mercury leakage.

4. Bleed the air out of the R-Z system and check for mercury leaks.

Using a 30-ml or larger syringe and a length of tubing, apply greater than 200 mmHg pressure to the mercury column. (A syringe gives faster and better control than a cuff and a bulb for this purpose, but the technician must be careful not to pull negative pressure.) If a cuff is used, it can be wrapped around a one pound coffee can. Watch the rise of mercury in the chamber, and maintain or increase the pressure until the mercury rise into the narrow vertical stem at the top of the chamber. If mercury does not enter the stem despite prolonged high pressure, deflate the cuff and repeat, after slightly opening the thumbscrew at the top of the stem. This will permit escape of any trapped air. When the mercury has entered the stem, close the thumbscrew firmly (but not excessively tight) and deflate the cuff.

5. Verify the maximum "zero" obtainable

    - The bellows valve should be in the "OPEN" position, and no pressure should be in the cuff. The cam should rotate freely.
    - Set the cam manually in such a position that the level on the end of the cam will contact the moving wall of the chamber after the shortest possible displacement of this wall toward the cam. (This position draws the least mercury into the reservoir and produces the highest "zero" level for the amount of mercury in the device at this time.)
    - Inflate the cuff above 200 mmHg and maintain it at this pressure until the chamber wall has come to rest against the bevel of the cam.
    - Turn the valve to "CLOSE," wait a full five seconds, and deflate and disconnect the cuff.
    - Record the zero level it should compare closely (within 4 mmHg) with the value on the label on the face of the manometer.

6. Verify the minimum "zero" obtainable

    - Repeat exactly as for (5) above, except set the cam so that the moving wall of the reservoir will move its maximum distance before contacting the cam. (This position draws the most mercury into the reservoir and produce the lowest "zero" level for the amount of mercury in the device at this time.)
    - Ensure that full pressure in the cuff is maintained until the wall of the chamber comes to rest against the bevel of the cam; this may take several seconds.

- Turn the bellows valves to "CLOSE," and deflate and disconnect the cuff.
- Record this zero level; it should match the value determined when the machine was calibrated, which is listed on the label.

7. Adjust zero levels if needed

Changes of zero levels are due either to loss of mercury or to air leakage at the bellows air bleed screw; accuracy of readings is not affected. To adjust zero levels, however, mercury must be added or removed from the system.

CAUTION: Mercury vapor is very toxic: Tiny droplets vaporize more rapidly than bulk. All loose mercury must be collected and inactivated. One effective and convenient product for mercury vapor reduction is HgX, a powder produced by Acton Associates, 1180 Raymond Boulevard, Newark, NJ 07102. It is recommended that all work be done in a container such as a plastic dishpan when mercury is to be transferred, that gloves and lab coat be worn, and that the area is well-ventilated.

If the minimum zero level is below 0:

- Open the bellows control valve and the valve at the top of the mercury reservoir, unscrew and remove the knurled cap at the top of the manometer column, and remove the air bleed screw at the top of the bellows chamber.
- Pour clean mercury into the top of the manometer tube, using a hypodermic syringe barrel or tight paper cone as a funnel. (As Baum writes, mercury can be cleaned of floating dirt and oxides by pouring it through a rolled cone of ordinary scratch paper with a pinhole at its apex. Note that some mercury will stick on and in the paper, so handle with care). About 400 grams (or 14 ounces) of mercury are needed to fill an instrument for a zero range of near 10 to 30 mm.
- Firmly screw the knurled cap onto the top of the manometer column, and apply pressure to the mercury reservoir until the mercury rises into the vertical air column at the top of the bellows chamber. Tighten the air bleed screw quickly and firmly, while the mercury is a short distance into the vertical air column.
- Apply enough additional pressure to raise the mercury to near the top of the manometer column (if it is not already that high); then release the pressure, thus to collect mercury droplets and clear the column of air bubbles. There are likely to be air bubbles trapped on the walls of the plastic tube at the bottom rear; these can sometimes be removed by tapping the tube sharply, but they are, at any rate, of no consequence.
- Determine zero range and adjust as needed.

If the minimum zero level is greater than 4 or the maximum is greater than 24:

- Unscrew and remove the knurled cap from the top of the manometer column. Using a syringe with a small tube, such as a catheter, remove the mercury from the manometer.

8. Check whether the spin wheel and cam spin freely.

    - Turn the bellows valve on the front of the manometer to "OPEN" and allow the wall of the chamber to move back to its resting position.
    - Spin several times the rubber-rimmed wheel used in setting the "zero" level for each reading. Note whether the cam spins freely, and whether it is excessively loose.
    - Adjust the spin by slightly loosening or tightening the mounting screw at the end of the cam.
    - After any such adjustment, recheck the spinning wheel repeatedly to ensure against tightness or looseness of the cam.

If spin wheel and cam are stuck (with bellows control cock open and all pressure released) or the rise of the mercury column is jerky as pressure is raised, there is usually binding or friction between the bellows plate center boss and the centering pin. Accuracy of readings has not been affected. A drop of good, light machine oil takes care of most such problems.

9. To remove the manometer column for cleaning or for inspection of it and of gaskets:

    - Set the cylindrical cam for maximum bellows volume, and open the bellows control valve.
    - Raise the reservoir pressure to about 280.
    - Close the bellows valve, and release pressure on the reservoir.
    - Tilt the RZM to the right (reservoir on down side) until all mercury has disappeared below the manometer column. Close the reservoir valve (handle to front). Rest the RZM on its right side, with the spin wheel above the table surface.
    - The manometer column may now be removed.

10. Maintenance requirements are minimal, but essential.

    - A very occasional drop of light machine oil is recommended on moving parts, including the bellows plate centering pin.
    - Do not, however, oil the bellows control valve stem or the mercury reservoir valve.
    - Ensure that moving parts are free without too much slack.

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- If pre-exercise heart rate is <40 or >110 beats/minute, do not perform treadmill test. Test may be rescheduled and performed when pre-exercise heart rate is in the correct range.
- If the test is discontinued early, proceed directly to cool down. If the test is discontinued because the participant is experiencing chest pain, cool down rapidly so that participant can dismount safely and staff can attend to his symptoms.

Summary of changes between Version 1.1 and 1.2:

- Added a step to estimate the number of revolutions per minute to treadmill qc procedure

Summary of changes between Version 1.2 and 1.3:

- Corrects calibration step 7calculation of belt speed to 6 times the belt length as the distance factor
- Corrects numbering of step references in calibration steps 8 and 9.
- Adds instruction to call service contractor where appropriate
- Adds instructions for creating measurement device with tri-square and level, and how to use it.

Summary of changes between Version 1.3 and 1.4:

- Updates staff certification procedure to show that master trainer (or backup master trainer) observes staff performing treadmills quarterly while in use, rather than monthly.

Summary of changes between Version 1.4 and 1.5:

- Confirms that heart rate should be monitored continuously during the procedure, and test should be terminated immediately if heart rate equals or exceeds 85% of age-predicted maximum.

18. Fitness Assessment

Introduction

A submaximal treadmill exercise test will be used to estimate cardiorespiratory fitness from the participants' heart rate response to a set workload. The underlying assumption for using this procedure is that as an individual's fitness level improves, heart rate at a set workload (e.g., HR at 3 mph) will be lower. The advantages of using this method are that no extrapolation is performed to estimate cardiorespiratory fitness, which has error associated with it, and no assumptions are made regarding a participant's maximal heart rate.

Blinding

It is preferred that the treadmill test be conducted by a blinded staff person. When this is not possible, treadmill testing may be conducted by an unblinded staff person who is not doing intervention visits or taking outcome blood pressure measurements.

Treadmill Protocol

Background

The treadmill protocols are devised based on the following assumptions:
1. Protocol to not exceed moderate intensity, since the intervention goals to all individuals are for moderate intensity, with vigorous intensity for those who qualify and are interested.
2. The protocol is based on estimated maximal cardiorespiratory fitness (METs) based on 50th percentile norms for age and sex.
3. The treadmill walk takes 10 full minutes. (Total time for the test including preparation is 20-25 minutes).

There are different protocols for men and women between the age of 20 and 39 years, 40 and 59 years, and 60 years and over. The protocols are listed in Appendix 1 at the end of the chapter.

The treadmill protocols are devised to have one workload in the light intensity category and one in the moderate intensity category. Each stage is for 3 minutes. There is a 2-minute warm-up before Stage 1 and a 2-min cool down after Stage 2 . Each participant should be on the treadmill for 10 minutes.

Required equipment and materials

- Any brand of treadmill as long as it can be calibrated for speed and incline
- Polar Vantage XL or other brand heart rate monitor able to keep a continuous digital read out
- Heart monitor extension strap for larger people (need several, elastic is not very resilient and gets stretched out easily)

- Stethoscope (any brand or style that is capable of a clinically valid measure)
- Standard sphygmomanometer (any brand or style that is capable of a clinically valid measure. If using a mobile mercury, will need a long BP tube)
- Wide tape (paper type like used in lab) to hold BP cuff from sliding down participant's arm.
- Large timer
- Towel and water bottle for participant after test
- Treadmill Protocol table (Appendix 3)
- Fitness Test Form (Form #26)
- Ratings of Perceived Exertion (RPE) Scale (Appendix 4 – make into a poster-sized chart and place in front of treadmill)

Preparing the participant for the test

Participants should be given basic instructions when the visit for the test is schedule. They need to wear comfortable clothing with loose sleeves and athletic or rubber soled shoes with socks.

Clinics should keep extra clothing (eg. Scrub tops) for participants who are not dressed appropriately.

Treadmill Procedures

1. **Welcome participant and ask if he/she has ever walked on a treadmill before.**
   a) If not, reassure the participant that it is very easy and all of the walking will be "at an effort level where you can speak and breathe comfortably."
   b) If not, give a brief demonstration of how to walk on a treadmill (this should take less than one minute).
2. **Explain the objective of the test to the participant.** See Appendix 1 for instructions and a sample script. Important points to cover are:
   a) The test is sub-maximal ("a level where you can speak and breathe comfortably").
   b) There is a 2-minute warm-up, 2 stages of progressive workload in which the speed and grade will increase slightly, and a 2-minute cool-down. The participant will be on the treadmill for 10 minutes.
   c) Heart rate will be monitored continuously; blood pressure will be monitored at the end of each stage. This is not a "score" for the participant, just an assessment of their heart rate.
   d) If heart rate or blood pressure goes too high (see item #13 p.18-5), the test will be terminated.
   e) If the participant has any chest pressure, dizziness, or other symptoms, the participant should inform the technician and the test will be terminated.
3. **Explain the Ratings of Perceived Exertion (RPE) Scale.** The scale should be displayed near the treadmill. Instruct the participant that you will be asking them how hard they feel like they are working during the last minute of each stage. See Appendix 2 for participant instructions.

4. **Prepare participant for test**
   a) Place heart rate band on participant using the procedure described by the manufacturer. For example, if using Polar heart rate bands and monitors: Put clean Polar heart rate band around participant's chest (below bra line for women). The "Polar" brand name should be in the center-front. The band may be moistened with water before placing it on the participant to hasten receiving heart rate information. Touch heart rate watch to "Polar" name on chest band to activate the heart rate.
   b) Apply the correct size BP cuff to the participant's arm at heart level. Either arm can be used. Use paper tape to maintain in position throughout the test.
5. **Seat participant for 5 minutes.** While the participant is seated:
   a) Fill out the participant's ID and the date of the visit on the Fitness Test Form (#26)
   b) Compute predicted maximal heart rate (= 220 - age) and 85% predicted maximal heart rate (= 220 - age) * 0.85. Record this information on the Fitness Test Form (#26).
6. **After the 5 minutes is up, measure pre-exercise blood pressure and record on the Fitness Test Form.**
7. **Measure pre-exercise heart rate and record on the Fitness Test Form.** If the pre-exercise heart rate is <40 or >110 beats/minute, do not perform the treadmill test and refer the participant to his physician for follow-up. The test may be rescheduled and performed at a time when the pre-exercise heart rate is in the appropriate range.
8. **Guide participant to the treadmill:** use appropriate protocol depending on participant's age and sex. Participants should be told they cannot hold on to the handrails (after initial balance is established).
9. **Refer to Appendix 3 for the correct age and gender protocol**
10. **Program treadmill for 2-minute warm-up at appropriate speed.**
11. **Stage 1:** Increase treadmill pace and incline at 1:55. Record heart rate at 2:50 and 3:50. Measure blood pressure and RPE at 4:20. Record heart rate again at 4:50. Record blood pressure and heart rate on Fitness Test Form.
12. **Stage 2:** Increase treadmill grade at 4:55. Record heart rate at 5:50 and 6:50. Measure blood pressure and RPE at 7:20. Record heart rate again at 7:50. Record blood pressure and heart rate on Fitness Test Form (#26).
13. **Cool down:** Decrease treadmill speed and grade at 7:55. Record cool down heart rate at 9:50. After a 3 minute seated rest, record blood pressure and post exercise heart rate on Fitness Test Form.
14. **Continue the test until completion or if criteria for terminating the protocol are met . Criteria are:**
   a) Participant heart rate $\geq$ 85% of age-predicted maximal heart rate at any time during the fitness test. Record this heart rate in the next available field for heart rate on Form #26.
   b) Blood pressure greater than 240 mmHg systolic or 115 mmHg diastolic.
   c) Participant complains of chest pressure, dizziness, or other symptoms.
   d) Participant RPE > 17

15. **If any criteria for terminating the protocol are met (see 14 a-d), then proceed directly to the cool down stage of the procedure.** If the test is discontinued because a participant is experiencing chest pains, accelerate the cool down by slowing the treadmill as rapidly as possible so that participants can dismount safely and staff can attend to their symptoms.

Safety Precautions

Safety precautions for the exercise testing will include training clinic staff to handle any emergencies that may arise. All clinical center staff should be aware of the procedures to follow should a participant experience a coronary event during the administration of the test. All technicians responsible for administering the treadmill test will receive formal training in CPR and will hold a valid certificate from the American Heart Association or another organization that provides training. Emergency telephone numbers should be prominently posted near the telephone.

Training, Certification, and Quality Assurance

Certification of a master trainer for each clinical site is done annually at a central location. At that time the study wide trainer reviews the appropriate techniques for measuring and recording the treadmill results.

All technicians take duplicate measurements on two individuals. Technicians are certified to

- Explain the test objective and safety procedures
- Explain the RPE chart to the participant
- Perform pre-test calculations (age predicted MHR, 85% MHR)
- Perform test preparation procedures (heart rate monitor, BP cuff placement, resting BP and pulse)
- Select pace and incline appropriate for participant's age and gender
- Measure exercise blood pressure
- Measure exercise pulse
- Measure exercise intensity by recording the participant reported RPE at the correct time
- Perform appropriate and timely adjustment of treadmill pace and incline
- Accurately complete the Fitness Test Form (#26)

The master trainer will then go back to the clinical site and train other staff as needed to do the treadmill protocol. For each person trained, the following form is completed by the master trainer and copies are sent to the Coordinating Center:

- Form #326, Fitness Test Certification Form

The master trainer (or backup master trainer) will also observe at least one treadmill testing session per technician each quarter (Form #326) while fitness tests are being conducted.

Treadmill Calibration

The equipment selected for exercise testing must be reliable, and allow for calibration every 3 months or 50 hours of use, whichever comes first. The resulting quality control allows one to evaluate the effectiveness of an exercise program, or simply to establish the fitness levels of those beginning an exercise program. This section is meant to be instructive and not a replacement for the specific procedures recommended by the manufacturer.

Treadmill

The treadmill is one of the most common pieces of equipment used to study exercise responses. The intensity of the exercise can be altered by changing the speed and/or grade. Reasonable results depend on accurate grade and speed settings.

Speed Calibration

Method 1. In some older treadmills, a mechanical counter is attached to the rear of the treadmill with a micro switch suspended over the treadmill belt. As the belt moves around the drums, an elevated surface on the outside edge of the belt triggers the switch. If the belt length (in meters) and the number of times the belt moves past the switch per minute are known, belt speed can be calculated in meters per minute ($m \cdot min^{-1}$). It is possible to use the same procedure on any treadmill by doing the following:

1. Using a meter stick, measure exact length of the belt, and record the value.
2. Place a small piece of tape on the belt surface near the edge, or mark the surface with a pen.
3. Turn on the treadmill to a given speed, using the speed control.
4. **Estimate the amount of revolutions per minute.** Count the number of belt revolutions in one minute by counting the number of times the piece of tape on the belt passed a fixed point, i.e., the back roller of the treadmill. Use a digital timer with an audio alarm to time 60 seconds, while the observer watches the belt and counts rotations. Alternatively, use two staff, one to count belt revolutions and the other to observe time on a stopwatch: start counting with "zero" and start your watch as the tape first moves past the fixed point.
5. Convert the number of revolutions to revolutions per minute as follows:
   - use a stopwatch to measure the exact time, in seconds, required for the belt to complete the number of revolutions observed in step 4.
   - convert this time in seconds and revolutions per minute into revolutions per minute.

6. For example, if the belt made 33 complete revolutions in 58 seconds:

   58 sec ÷ 60 $sec \cdot min^{-1}$ = .967 min.
   So, 33 rev ÷ .967 min = 34.14 $rev \cdot min^{-1}$

7. Multiply the calculated $rev \cdot min^{-1}$ (step 6) times the belt length (step 1). The product is the belt speed in $m \cdot min^{-1}$. For example, if the belt length were 2.532 m:

$34.14\ rev \cdot min^{-1} \times 2.532\ m \cdot rev^{-1} = 86.4\ m \cdot min^{-1}$

8. To convert $m \cdot min^{-1}$ to miles per hour ($mi \cdot hr^{-1}$), divide the answer in step 7 by 26.8 $m \cdot min^{-1}$ per $mi \cdot hr^{-1}$:

   $86.4\ m \cdot min^{-1} \div 26.8\ m \cdot min^{-1}\ per\ mi \cdot hr^{-1} = 3.22\ mi \cdot hr^{-1}$

9. The value obtained in step 8 is the actual treadmill speed in $mi \cdot hr^{-1}$. If the speed indicator does not agree with this value, adjust the dial or display to the proper reading using directions in the manual that accompanied the treadmill, or call the service contractor.
10. Repeat for a number of different speeds to ensure accuracy across the speeds used in test protocols.

Method 2. If your treadmill is equipped with a device to count the revolutions of one of the drums, the counter may be used to check the accuracy of the speedometer. Simply set the counter to zero, set the treadmill to the desired speed, and operate the counter for exactly 1 minute. Check the instruction manual for your treadmill to make sure of the relationship between the $rev \cdot min^{-1}$ and speed in $mi \cdot hr^{-1}$. Adjust the speedometer to the correct setting, or call the service contractor. This method is accurate only if the treadmill belt is properly adjusted and does not slip.

Elevation Calibration

The manual that comes with the treadmill describes how to calibrate the grade with a simple "carpenter's level" and a "square." This calibration procedure is shown below.

1. Use a carpenter's level to make sure that the treadmill is level and check the "O" on the grade dial under these conditions (with the treadmill electronics "on"). If the dial does not read "O," follow instructions to make the adjustment.
2. Elevate the treadmill so that the grade dial reads approximately 20%. Measure the exact incline of the treadmill as shown in Figure 1. When the level's bubble is exactly in the center of the tube, the "rise" measurement is obtained. Calculate the grade as the "rise" over the "run" (tangent 0), and adjust the treadmill meter to read that exact grade, or call the service contractor. For example, if the "rise" were 4.5 inches to the "run's" 22.5 inches, the fractional grade would be:

   Grade = tangent 0 = rise ÷ run = 4.5 in ÷ 22.5 in = 0.20 x 100% = 20%

3. Repeat this process at grades between 0 and 20^{o} (0-34%) to make sure the meter is correct.

An alternative measurement device can be created with a 48-inch level, an adjustable tri-square and a 1-½ inch C clamp. Attach the tri-square to one end of the level so that the flat surface of the 90-degree tri-square angle rests on the long surface of the level and the 12-inch ruler part of the tri-square is flush with the level's end. The C clamp is used to hold the tri-square in this position.

1. With the measurement device assembled the 48-inch level is placed on the surface of the treadmill so that the tri-square end is at the rear of the treadmill. At low ranges of incline the

device will need to be placed on the treadmill so that the tri-square is on the upper surface of the level. At high ranges of incline the device will need to be reversed.

2. Verify that the treadmill is flat. With the treadmill reading 0 grade, place the device on the surface of the treadmill. The horizontal bubble in the center of the level should be in the mid-point of the glass, between the lines.

3. Measure various grades of incline. Increase the incline. Hold the level so the bubble shows it is horizontal. Adjust the ruler on the tri-square with the thumbscrew so the lower end touches the surface next to the treadmill. The rise is measured on the tri-square ruler were the bottom edge of the level intersects the ruler. The run is the length of the level. The measurement limit of this device with a 48 inch ruler is a 25% incline. If the tri-square ruler measured the rise at 7 inches the fractional grade would be:

Grade = tangent 0 = rise run = 7 in 48 in = 0.145 x 100% = 14.5%

This "Rise" over the "Run" method is a typical engineering method for calculating grade – the vertical rise divided by the horizontal run. This method gives the tangent of the angle (the opposite side divided by the horizontal distance, as shown in Fig. 1). Although this tangent method is not exactly correct, it is a good approximation for grades less than 20% or 12^{o} (see Table 18-1).

Fig. 1. Calibration of grade by tangent method (rise run) with carpenter's square and level

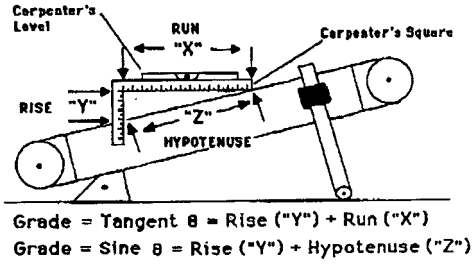


Fig. 2. Calibration of grade for fixed rear axle treadmill by sine method (rise hypotenuse)

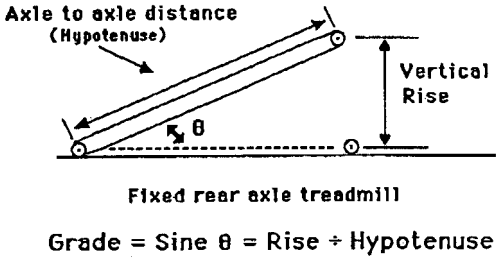


Table 18-1. Table of Natural Sines and Tangents

Degrees	Sine	% Grade	Tangent	% Grade
0	0.000	0.0	0.0000	0.0
1	0.0175	1.7	0.0175	1.7
2	0.0349	3.5	0.0349	3.5
3	0.0523	5.2	0.0524	5.2
4	0.0698	7.0	0.0699	7.0
5	0.0872	8.7	0.0875	8.7
6	0.1045	10.4	0.1051	10.5
7	0.1219	12.2	0.1228	12.3
8	0.1392	13.9	0.1405	14.0
9	0.1564	15.6	0.1584	15.8
10	0.1736	17.4	0.1763	17.6
11	0.1908	19.1	0.1944	19.4
12	0.2079	20.8	0.2126	21.3
13	0.2250	22.5	0.2309	23.1
14	0.2419	24.2	0.2493	24.9
15	0.2588	25.9	0.2679	26.8
20	0.3420	34.2	0.3640	36.4
25	0.4067	40.7	0.4452	44.5

The “correct” method expresses grade as the sine of the angle (sin 0), where sin 0 equals the vertical rise (opposite side) over the hypotenuse [sin 0 = rise ÷hypotenuse (see Fig. 1)]. This method should be used to calculate steep grades (above 20%). The vertical rise can be calculated simply for a treadmill with a fixed rear axle. Simply measure the change in the height of the front axle above the horizontal (rise). When you divide this by the axle length (hypotenuse), you have the grade, expressed as a fraction (Fig. 2).

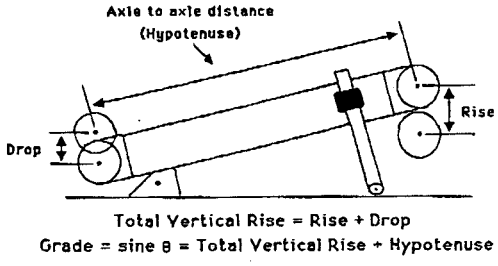
For a treadmill with movable rear and front axles, the vertical rise is equal to the sum of the rise of the front axle and the drop of the rear axle (Fig. 3). When this total is divided by the axle-to-axle length, the quotient is the grade, expressed as a fraction. For example, if the front axle height, is 0.327 m on the level (0% grade) and 0.612 m at the unknown grade, the front axle rise is 0.612 – 0.327 = 0.285 m. Similarly, if the rear axle height is 0.324 m at 0% grade and 0.299 m at the unknown grade, the drop is 0.025 m. The total vertical rise is then equal to the “rise” plus “drop” or 0.285 + 0.025 = 0.31 m. If the axle-to-axle length (hypotenuse) is 2.095 m, the grade can be calculated as:

Grade = total rise ÷ hypotenuse = 0.31 m ÷ 2.095 m = 0.148 x 100% = 14.8%

Note: For low grades (below 20%), the sine method gives a value that is nearly equal to the tangent method, so that method does not matter (see Table 18-1). For steep grades, one can also use the “rise” over the “run” method (using the carpenter’s square) to obtain the tangent value

and then look across the table to obtain the correct sine value to set on the treadmill dial. For example, if the "rise" over the "run" method yielded 0.268 or 26.8% (tangent), the "correct" setting would be 25.9% (sine). The latter value is set on the grade dial of the treadmill.

Fig. 3. Calibration of grade for movable rear axle treadmill by sine method (rise hypotenuse)



Appendix 1: Participant Instructions Script

Following is the information that should be explained to participants. These instructions can be read verbatim to the participant, or explained in a conversational manner. However, the points that must be covered are:

1. The test is submaximal.
2. There is a 2-minute warm-up, 2 stages of progressive workload for 3 minutes each stage, in which the speed and grade will increase slightly, and a 2-minute cool-down. The participant will be on the treadmill for 10 minutes.
3. Heart rate will be monitored continuously; blood pressure will be monitored at the end of each stage.
4. If the participant has any chest pressure, dizziness, or other symptoms, the participant should inform the technician and the test will be terminated.

PREMIER Exercise Test Script

Introduction and Overview

Today we're going to ask you to complete a fitness test on a treadmill that will evaluate your body's response to exercise. We will need you to walk on a treadmill for 10 minutes at an intensity level where you can speak and breathe comfortably. Have you ever walked on a treadmill? (If not, demonstrate.) There are a few guidelines I need you to remember throughout the test:

1) Straddle the belt when you step on the treadmill, making sure both feet are not touching the belt. After the belt starts you can slowly step on and begin walking
2) You can hold the rail to gain initial balance but when I tell you the test is beginning I will need you to release the railing
3) Never turn your head or body to the side or the back when you are walking on the treadmill
4) Let me know if anytime during the test you experience feelings of illness, nausea, shortness or breath, dizziness, or pain in your chest, jaw, and arms. If any of these symptoms occur, we'll stop the test immediately
5) Unless you need to report any unusual symptoms, I ask that you remain quiet during the test (especially when we are measuring your BP)

Preparation and Warm-up

What I first need you to do is rest quietly for 5 minutes. Then I'll measure your resting heart rate and blood pressure. After that, you can step on the treadmill and we'll let you warm up with a 2-minute walk at 2 mph.

Performance and Monitoring

The test will consist of 2 stages that will last 6 minutes. During those 6 minutes, I will gradually increase the speed and incline of the treadmill every 3 minutes. I'll be sure to let you know

during the test when these changes will occur. As a safety precaution, I will also be periodically measuring your heart rate and blood pressure. To do this, I will need you to hold out your arm when I indicate that I need a BP measurement.

Ratings of Perceived Exertion Scale

One last thing I will ask you to report during the test is your perceived exercise intensity. To make this easier, I have a chart with a number scale from 6-20. Along side the numbers are words that describe different levels of physical exertion. Two times during the study I will ask you, "how hard to you feel you are working?" I will need you to look at this chart, find the words that best describe how the work feels at that point in time, and tell me the number that corresponds with your feelings. For example, if I'm walking on the treadmill at a certain pace and I felt as though I was working very light, I would estimate that my exercise intensity is at number 9. Keep in mind that as you look at the chart, there are no right or wrong numbers, only a number that represents how hard you feel you are working at a particular point in time.

Ending the test

After you've completed both stages of the test I will decrease your speed and incline and let you walk slowly for a 2 minute cool down period. Then you can sit down to rest for about 3 minutes and after that I'll measure your blood pressure and heart rate one last time. Do you understand everything that I've explained? Do you have any questions before we get started?

Appendix 2: Ratings of Perceived Exertion Summary of Participant Instructions

1. Try to estimate the degree of exertion as accurately as possible.
2. Do not underestimate or overestimate the exertion. Simply rate your feelings caused by the work at the moment.
3. The ratings should be based on your own evaluation of your total body feelings, and not on leg cramps, leg fatigue, or other localized sensations.
4. Use the attached expressions to help you rate your feelings.
5. Start at any point shown on the scale — there are no right or wrong numbers.

Appendix 3: Treadmill Protocols by Age and Gender

Men ages 20-39:	Warm-up:	2 MPH,	0%
	Stage 1:	3.3 MPH,	2% grade (4.4 METs)
	Stage 2:	3.3 MPH,	7% grade (6.7 METs)
	Cool-down:	2 MPH,	0%
Men ages 40-59:	Warm-up:	2 MPH,	0%
	Stage 1:	3 MPH,	2% grade (4.1 METs)
	Stage 2:	3 MPH,	7% grade (6.2 METs)
	Cool-down:	2 MPH,	0%
Men ages 60+:	Warm-up:	2 MPH,	0%
	Stage 1:	2.5 MPH,	2% grade (3.6 METs)
	Stage 2:	2.5 MPH,	7% grade (5.3 METs)
	Cool-down:	2 MPH,	0%
Women ages 20-39:	Warm-up:	2 MPH,	0%
	Stage 1:	3 MPH,	2% grade (4.1 METs)
	Stage 2:	3 MPH,	7% grade (6.2 METs)
	Cool-down:	2 MPH,	0%
Women ages 40-59:	Warm-up:	2 MPH,	0%
	Stage 1:	2.5 MPH,	2% grade (3.6 METs)
	Stage 2:	2.5 MPH,	7% grade (5.3 METs)
	Cool-down:	2 MPH,	0%
Women ages 60+:	Warm-up:	2 MPH,	0%
	Stage 1:	2 MPH,	2% grade (3.1 METs)
	Stage 2:	2 MPH,	7% grade (4.5 METs)
	Cool-down:	2 MPH,	0%

Appendix 4: Ratings of Perceived Exertion Scale

6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very Hard
18	
19	Very, Very Hard
20	

Your goal is to rate your feelings that are caused by the work and not the work itself. These feelings should be general, that is, about the body as a whole. We will not ask you to specify the feeling but to select a number that most accurately corresponds to your perception of your total body feeling. Keep in mind that there are no right or wrong numbers. Use any number you think is appropriate.

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Titles of this chapter, Forms #104, and #105 changed to “Food Interview” from “Diet Recall”

19. 24-Hour Food Interviews

Overview

Collection of 24-hour food interviews (originally called "diet recalls") will be used to assess the participants' baseline dietary intake and adherence to the PREMIER dietary guidelines. These interviews will be collected via telephone by dietary staff at Pennsylvania State University (PSU).

Two unannounced 24-hour diet recalls will be conducted between SV3 and the randomization visit to provide baseline dietary intake data. Two followup diet recalls will be conducted at 6 months and 18 months. Each pair of recalls will occur within a 3-week period, on non-contiguous days, one of which will be a weekend day.

Procedure

The procedure to be followed is the same for each set of recalls (baseline, 6 months, and 18 months).

Hand out materials to participants during their clinic visit

Clinic staff need to hand out and review the following materials with the participants:

Food Interview Instruction Sheet (Form #104): This contains background information about Penn State (so the participants know who will be calling them) and the diet recall process. This instruction sheet should be reviewed at SV3, and again at 6 and 18 months.

Poster: This has information participants will need during the call. Each participant will need to have their poster handy when they receive their phone call from Penn State. The posters will be purchased by Penn State and shipped directly to each site for distribution. Posters will be handed out at SV3. Some participants may need replacement posters at 6 and 18 months.

Complete Convenient Times Schedule

This schedule (Form #105) is filled out by the participants to indicate how they can be reached and at what times they will be available. It also has space at the bottom for indicating special situations (participants who need to be paged, etc.). If a participant will be out of town during the entire calling period, be sure to get a number where they can be reached. If a participant can not be reached during the calling period, they will not be able to be randomized.

It is important to be sure that each participant identifies at least one time that they can be called for each day of the week.

This form will be completed at the SV3 visit and again at the 6 and 18-month visits.

There are three versions of this form, one for each time zone. It is important that sites use the correct form to ensure that participants can be reached for their recalls. The time slots that are available are:

	<-------Morning------->			<-------Afternoon ----->			< ------- Evening------ >		
Eastern (Baltimore and Durham):	9-10	10-11	11-12	1-2	2-3	3-4	4-5	6-7	7-8	8-9
Central (Baton Rouge):	8-9	9-10	10-11	12-1	1-2	2-3	3-4	5-6	6-7	7-8
Pacific (Portland):	6-7	7-8	8-9	10-11	11-12	12-1	1-2	3-4	4-5	5-6

Some issues that may come up when completing this form:

Work phones: Penn State can call participants at work, if that is the only way to reach them. However, clinic staff needs to be clear with participants that if they list a time when they can be called at work, they need to be able to interrupt their work for the 20 minutes or more that the recall will take.

Pagers: Penn State prefers not to contact participants via pagers because this reduces the randomness of the recall (the participant gets to decide when to call back). However, if there is a participant where this is the only way they can be reached, note this information on the bottom of the form and Penn State will make every effort to reach the participant via pager.

Fax schedules

The sites will fax the Convenient Times Schedules to Penn State as they are completed. Fax and phone numbers for Penn State are available from the staff directory on the PREMIER web site. Because participant names appear on this form, staff at clinical sites as well as at Penn State need to be careful to avoid breaches of confidentiality. Fax numbers should be dialed carefully, and these forms should not be left sitting on the fax machine unattended at either end of the transmission.

Selection of calling days

Penn State will randomly select the two days they will be calling. They will select one weekday and one weekend. Weekend will be defined as Saturday and Sunday for all participants, even if this is not the participant's normal "weekend". Penn State will make every effort to complete the two recalls on the appropriate days. If they have trouble reaching a participant, they may have to call on a different day. This means that a small percentage of participants will end up with two weekday or two weekend recalls.

Calls completed and sites notified

Penn State plans to complete most calls within 14 days. They will fax each site a list of completed recalls on day 16 or 17. To protect confidentiality, this fax will contain study ID numbers only, **not participant names**. Penn State will continue to try to complete the remaining recalls over the next week. Sites will be notified of each additional completed recall on a case-by-case basis. Any fax or e-mail **follow-up** communications between Penn State and the clinical sites should reference participants by study ID number, not participant names.

Each completed recall should be logged on the appropriate visit form. If the recall cannot be completed within the three-week window, the incomplete outcome should be logged on the visit form. For SV3, the information should be logged on the Pre-Randomization Checklist (Form #19). For the 6 and 18 month visits, the information should be logged on the 6 and 18 Month Visit Forms (#57 and #59).

Data file delivered to Penn State

After participants have been randomized, the coordinating center will ship Penn State a data file with dates of birth and gender for each of the participants. This information is needed for Penn State's analyses. This file will be delivered electronically, and will not contain any participant names or identifiers other than the study ID.

20. OTHER CLINICAL MEASUREMENTS 3

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Height: participant's buttocks must touch the wall or height board.
- Stadiometers: perform QC twice each year while in use. Time QC to precede the beginning of each new cohort.
- Title of Form #322 changed from "Quarterly Stadiometer Accuracy Check Form" to "Stadiometer Accuracy Check Form.
- Confirm accuracy of a fixed height measurement system if it appears to have moved from its original position.
- Scales: perform QC quarterly, rather than every other month.

Summary of changes between Version 1.1 and 1.2:

- Procedure added for off-site measurement of weight
- Procedure added for off-site measurement of waist circumference

20. Other Clinical Measurements

Height

Height measurement to the nearest 0.1 cm is taken by a certified PREMIER clinical staff member at the first screening visit. Height is measured in metric units with the participant standing on a firm, level surface which is at a right angle to the vertical board of the height measurement device. A height board mounted at a 90° angle to a calibrated vertical height bar is used. Prior to the beginning of screening for the first cohort, use a level to check that the floor is level and that the wall on which the height bar is mounted is straight. Check that the vertical height bar is mounted at a 90° angle to the floor.

Instruct the participant to remove shoes and headgear (hats and unusually large hairpieces) and to stand erect with feet flat on the floor and both heels together, touching the base of the vertical board. The participant stands erect with back, shoulder blades, and buttocks in contact with the vertical height board. If the participant cannot be positioned so that all of the above are in contact with the board, position so that the participant is standing erect with buttocks in contact with the board. The participant's weight is evenly distributed on both feet, and arms remain relaxed at the sides with palms facing inward. The participant stands facing straight ahead with her head in the horizontal (Frankfort) plane. The eyes of the examiner should be at the same level as the height indicator bar to obtain the most accurate measurement (Figure 1, Frankfort Horizontal Plane).

Ask the participant to inhale deeply and maintain a fully erect position without altering the load on the heels. Bring the height board down snugly, but not tightly, on the top of the participant's head. Record the height to the nearest 0.1 centimeter on the SV1 Visit Form (Form #3).

Weight

Body weight measurements are taken to the nearest 0.25 lb by certified PREMIER clinical staff throughout the study. The weight measurement taken at SV1 is used with the height measurement to calculate body mass index (BMI, kg/m^2) to exclude candidates whose body mass index is in excess of 45.0 kg/m^2 or under 18.5 kg/m^2.

Instruct the participant to remove shoes, headgear, coat, etc., and heavy items in the pockets (e.g., keys or wallet) in order to be weighed in light indoor clothing. All body weights in PREMIER are measured on a balance beam or digital scale, which is placed on a firm, level surface. If this surface is carpeted, a sheet of wood or hard plastic should be placed beneath a balance beam scale.

Ask the participant to stand in the center of the scale platform, since standing off-center may affect the weight measurement. It is suggested that marks be made on the platform to insure the proper position of the participant's feet. The participant should stand with arms relaxed at the sides, head erect, and eyes looking straight ahead.

Balance Beam Scale:

Be sure the scale is balanced so that the indicator is at zero when no weight is on the scale. Before each weight is measured, the sliding scale weights must be moved to zero. Adjust the weight on the indicator until it is balanced, and record the results to the nearest 0.25 lb. Use extreme care in adding the lower beam weight to the upper beam weight, as they use different increments. Advise the subject to remain standing in position on the scale until the weight has been recorded. This eliminates the possibility of the weight measure being accidentally altered by the balance beam moving as the subject dismounts.

Digital Read-out Scale:

Make sure the scale reads "0" before the subject stands on the measurement platform. When the digital readout stabilizes, record the observed weight to the nearest 0.25 lb.

Weight for Home or Office Visit

The UC-300 portable scale is the only device approved to obtain weight at visits conducted outside the clinic setting (i.e. in a participant's home or office). Validate the scale by comparing it to the in-clinic calibrated scale before and after the visit.

- Prior to the home visit, a staff member should weigh herself on the calibrated clinic scale and then immediately on the portable scale. If portable scale weight is not within 4 pounds of the calibrated scale, the portable scale should not be used for the home/office visit.
- When measuring weight, the scale is to be placed on a non-carpeted surface. If only carpeted surfaces are available, place a sheet of wood or hard plastic between the carpet and scale prior to obtaining a weight.
- Upon return from the home/office visit, re-check the portable scale against the clinic scale. If the scales differ by more than four pounds, that home/office measurement cannot be used.

Waist (Abdominal) Circumference Measurements

Waist circumference measurements are taken with an anthropometric measuring tape. Skin should show no marked compression. BE CERTAIN THAT THE TAPE IS KEPT HORIZONTAL WHEN MAKING MEASUREMENTS. To make certain that the tape is kept horizontal, it is best to have an assistant present when taking the measurements, or to mount a full length mirror on a wall approximately 1½ to 2 feet from the floor. Since circumference measurements are made over the participant's undergarments only, a hospital gown may be worn during measurements but the tape should go under the gown. Take one measurement, recording it to the nearest 0.1 cm, then remove the tape from the participant and reposition to take the second measurement.

Overview of Procedure

Waist circumference is measured from the horizontal plane at one centimeter (1cm) above the navel (measure 1 cm from the top of the navel with a firm ruler and mark this spot in ink). This usually coincides with the narrowest circumference, but has the added advantage of being easily reproducible. Be sure that the tape is kept horizontal when making the measurement (either in front of a mirror or with an assistant). Measurement is made with the participant standing erect, abdomen relaxed, arms at the side, and feet together with weight equally divided over both legs. Tell participants to breathe normally, to breathe out gently at the time of measurement, and not to hold in his abdomen or hold his breath (i.e., at the end of a normal expiration of air). At the R/I Visit, record the value obtained on the Randomization Checklist (Form #60). At the 6 Month Follow-Up Visit, record the value obtained on the 6 Month Visit Form (#57). At the 18 Month Follow-Up Visit, record the value obtained on the 18 Month Visit Form (#59).

Waist Circumference for Home or Office Visit

To measure the waist circumference at a home or office visit, staff will need to make prior arrangements with the participant.

- Arrange to perform measurement in a safe area to insure both privacy for the participant and safety for the staff (i.e. not in someone's bedroom, possibly the office bathroom)
- Ask participant if a mirror is available (If neither an assistant nor mirror is available, turn the participant from side to side while holding the tape securely to check tape position).
- Ask participant to wear clothing that will allow her/him to expose the navel area.

If satisfactory arrangements can be made, follow the in-clinic procedure for waist circumference.

Equipment Maintenance and QC

Scales

Scales are certified at the start of the trial by the local Bureau of Weights and Measures or an equivalent body. Re-certification must be completed annually thereafter and posted in the appropriate column of the Weight Scale(s) quarterly check and Yearly Certification Log (Form #310), along with any documents provided by the inspector. Form #310 is also used to record scale accuracy. The scale is tested quarterly at two levels to ensure accuracy in the range of weights measured during the trial. The lower range is checked using 20-30 kg weights. The upper range is checked using 40-50 kg weights.

1. The technician is weighed on the scale first and this weight recorded.
2. The lower weight is then placed on the scale and this weight recorded.
3. The technician then gets on the scale with the lower weight and this weight recorded.
4. The sum of the value obtained in step 1 and the value obtained in step 2 should equal the weight measured in step 3.
5. Next, the higher weight is placed on the scale by itself and this weight is recorded.

6. The technician now gets on the scale with the higher weight; this combined weight is recorded.
7. The sum of the value obtained in step one and the value obtained in step 5 should equal the weight measured in step 6.

These records are requested periodically and checked during site visits. Scales which fail to meet standards within 0.5 kg at any weight level should not be used for collection of study data and should be immediately reconditioned and re-certified by the Bureau of Weights and Measures or an equivalent body. All scales used must be uniquely identifiable, either by serial number or by a study-specific number printed in indelible ink.

Stadiometers

If height is measured using a stadiometer, perform QC twice each year while in use, timed to precede the beginning of recruitment for each cohort. Stadiometer QC during cohort 4 would occur just prior to cohort 4 recruitment, and again every 6 months while in use. to verify accuracy as follows. This information is recorded on the Stadiometer Accuracy Check Form (#322). If the stadiometer cannot be successfully calibrated, it may not be used for participant height measurements.

1. Place a 600 mm (60 cm) height rod against stadiometer and lower the height gauge to the top of the rod.

2. If the counter does not record the correct length of the rod:
   - loosen by undoing the two metal retaining screws and pull away from the main fiber cog of the carriage;
   - turn until the counter records the true length of the metal rod;
   - press against the backplate so that the teeth of the counter cog and the carriage cog engage;
   - tighten the retainer screws;
   - move headboard up and down the backboard a number of times;
   - re-check calibration

3. When accurate, record recalibration on Form #322

Fixed height measurement devices

Monitor these devices for obvious signs that they have been moved. If the device appears to have moved from its original position, confirm accuracy of measurements from floor level. Remount if inaccurate.

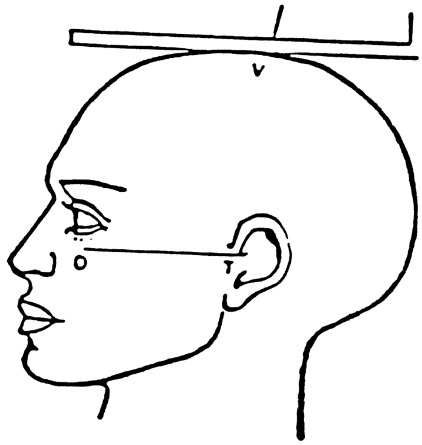
Certification of Trainers and Technicians

Certification of a master trainer is done annually at a central location. At that time the study wide trainer reviews the appropriate techniques for measuring and recording height, weight, and waist circumference.

All technicians take duplicate measurements on two individuals. The technician takes the first measurement of both the height and weight on the individual, then repeats the process for the second measurement of height and weight on the same individual. The average of the duplicate measurements on a given individual must be within 0.2 kg weight and 1 cm height of the master trainer's measurement. Both measurements on a given individual must be within 0.2 kg/1cm of each other. All technicians measure waist circumference twice on two individuals also. Average waist circumference measurements on a given individual must agree with the master trainer's measurement within 2 cm, and both readings on a given individual must agree with each other within 2 cm. Individuals at the sites may be trained as appropriate by the master trainers. For each person trained, the following forms are completed by the master trainer and copies are sent to the Coordinating Center:

1. Weight Certification Form (#309)
2. Weight Observation Checklist Form (#308)
3. Height Certification Form (#312)
4. Height Observation Checklist Form (#311)
5. Waist Circumference Certification Form (#314)
6. Waist Circumference Observation Checklist Form (#313)

Figure 1 Frankfort Horizontal Plane for Measuring Body Height



ORBITALE:	Lower margin of eye socket.
TRAGION:	Notch above tragus of ear or at upper margin of zygomatic bone at that point.
FRANKFORT PLANE:	Orbitale tragion line horizontal.

21. CENTRAL LABORATORY PROCEDURES 4

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Added procedure for CDC labs: folate, carotenoids, vitamin B-12.

Summary of changes between Version 1.1 and 1.2:

- Minimum amount of serum needed for CDC samples is 1 ml per vial.

Summary of changes between Version 1.2 and 1.3:

- If procedures for 24-hour urine refrigeration are not followed, urine samples stored for more than two days at room temperature are unusable.
- Added reference to additional specimen transport procedures in Chapter 27. Offsite Data Collection Visits.
- Updated shipping instructions to meet predetermined assay date.
- Updated contact person information at CLCS and BBI.
- Updated alert values for glucose and LCL-C.
- 8 ml purple cap transport vial for homocysteine not needed at 18 months

Summary of changes between Version 1.3 and 1.4:

- Updated contact person information at CDC on p. 21- 4 and 21-20.
- Updated statement on p. 21- 4 that states CDC shipment should not be sent to address stated on p.21-4 but to address on p.21-20.
- Updated shipping instructions for CDC on p. 21-20 to include timeframes for shipping samples, Premier Study Tracking # and primary contact persons for shipping and specimen questions.
- Added inclusion of Premier Study Tracking # in shipping paperwork to CDC on p. 21-19
- Added minimum levels of dry ice in CDC shippers on p.21-19.

- 21. Central Laboratory Procedures

Introduction

The Core Laboratory for Clinical Studies (CLCS) of Washington University Medical School will serve as the central laboratory for PREMIER. BBI (Biotech Research Laboratories) will serve as the repository for the PREMIER storage specimens. This manual contains the information needed to collect, process, and ship specimens to the laboratory for analysis and the repository for storage. Please review the manual before the beginning of the study and contact the laboratory or the repository if you have any questions or require additional information.

Contacts at CLCS

Customer Service (314) 362-3522

Laboratory Fax Number (314) 362-4782

Primary Contact: Clinical Studies Coordinator
Judy Jones (314) 747-1127

Laboratory Director: Thomas Cole, Ph.D.

Laboratory Manager: Connie Ferguson, M.T. (ASCP)

Information Systems Supervisor: Dave Gibson, B.S.

Technical Supervisor: Mike Macke, M.T. (ASCP)

U.S. Mail Address:

Core Laboratory for Clinical Studies
Washington University School of Medicine
660 S. Euclid Ave., Box 8046
St. Louis, MO 63110

Shipping Address: (UPS & FedEx)

Core Laboratory for Clinical Studies
Lipid Research
4940 Parkview Place
St. Louis, MO 63110

Contacts at CDC

Christine M Pfeiffer, Ph.D.
Chief, NHANES Laboratory
Centers for Disease Control & Prevention
4770 Buford Hwy. NE, MS F-18
Atlanta GA 30341-3724 USA

e-mail: CPfeiffer@cdc.gov
Phone: 770-488-7926
Fax: 770-488-4609

Note: CDC specimens are not shipped to above address. See p. 21-20 for a complete address.

Contacts at BBI

Primary Contact: Laboratory Manager
Carla Hansen (301) 208-8100 Fax: (301) 208-8829

Principal Investigator
Dr. Mark Cosentino (301) 208-8100

Shipping address: (UPS & FedEx)

Carla Hansen
BBI - Biotech Research Laboratories
217 Perry Parkway
Gaithersburg, MD 20877

Study Supplies

Supplies provided by CLCS

- Blood collection tubes
- Labels and vials for specimen aliquots
- Shipping and storage boxes for specimens
- Urine collection hats and jugs
- Blood collection kits for screening, 6 months and 18 months
- Shipping containers and supplies
- Pre-addressed Federal Express airbills, airbill pouches, dry ice labels, and instructions
- Disposable transfer pipettes

The CLCS will distribute specimen collection kits directly to each center as needed via UPS. These shipments require about 3-5 days shipping time. **Therefore, orders should be made at least a week in advance of the date that they are needed.** Requests for supplies can be made by telephone or fax to the CLCS Clinical Studies Coordinator. If making a request via fax, use the Request for Additional Lab Supplies (Form #315).

The provided supplies must be used only for this study. If a large number of redraws or abnormal situations occur, inform the CLCS of the need for replacement supplies. Each center will be responsible for maintaining an adequate inventory of supplies.

The CLCS will also provide the collection kits for the storage specimens. The BBI will provide the shipping container and supplies. The CC will contact the BBI after randomization to inform the repository of the number of specimens to expect from each site so they can send the correct number of shipping containers.

Supplies provided by CDC

- (1) 7-mL Hemogard-closure SST Vacutainers with no anticoagulant (pre-screened to ensure absence of background lead contamination).
- bar-coded labels for specimen vials ("VITA" and "SFOL") and paperwork
- 2.0-mL Nalge cryovials
- reusable Styrofoam insulated shippers and extra outside cardboard covers
- clear plastic packaging tape and dispenser
- white 9x9 grid cardboard storage boxes to place vials into for shipment
- large ziplock bags for enclosing the white storage boxes during shipment (to contain any leakage which might occur)

Supplies required at clinical sites

- Standard clinical centrifuge (a refrigerated centrifuge is preferred, but a non-refrigerated centrifuge is acceptable). The CDC lab requires a centrifuge capable of 1500 X G (2400-2800 RPM), with swing-out rotors.
- Ultra-low temperature freezer (-70C or colder, i.e., ultra low REVCO or equivalent). All blood specimens must be stored at -70C. If necessary, urine specimens may be stored in a non-cycling -20C freezer, for up to 30 days before shipping. Contact the CLCS if you do not have access to a -70C freezer.
- Dry ice for shipping.
- Federal Express pick-up service, UPS drop-off service
- Racks for tubes
- Phlebotomy supplies
- Distilled or de-ionized water
- Indelible markers for labels
- Biological waste bags
- 6 N HCl preservative for urine
- 2 L graduated cylinder for measuring urine volume
- Graduated pipettes for aliquotting urine

Preparing for the Visit:

Materials Needed

Visit-specific kits (see description below)
Visit and participant specific labels
Central Lab Collection Form- 24-Hour Urine (Forms #20, 62, 64)
CDC Form (#77)
Central Lab Collection Form- Fasting Blood (Form #21, 63, 65)
Central Lab Freezer Log – Blood and Urine Samples (Form #328)
Storage Lab Freezer Log – Blood Samples (Form #329)

Storage Lab Freezer Log – Urine Samples (Form #330)
Central Lab Duplicate Sample Form (Form #66) – if participant is part of the CLCS QC procedure

Description of Visit Kits used for CLCS Blood Draws

A single kit of blood collection supplies will be used for all visits (screening, 6 months, and 18 months). Labels will be sent separately for each visit.

Supplies:

2 x 10 mL SST Vacutainer tubes (red/gray top)
1 x 13 mL plastic pooling vial (red cap)
1 x 8 mL plastic transport vial (red cap)
3 x 2 mL plastic freezing vials (red cap)

2 x 10 mL EDTA Vacutainer tubes (purple top)
1 x 13 mL plastic pooling vial (purple cap)
1 x 8 mL plastic transport vial (purple cap – not needed at 18 months)
3 x 2 mL plastic freezing vials (clear cap)

Buffy Coat (screening only):
1 x 2 mL plastic freezing vial (purple cap)

Additional materials from CDC:

1 x 7mL Hemogard-closure SST Vacutainers (pre-screened to ensure absence of background lead contamination). If SST Vacutainers are used, it is much easier to transfer the serum to the vials and contamination with RBCs is minimized. Ordinary red-top Vacutainers may be used, but greater care is required for serum transfer.
2.0-mL Nalge cryovials

Description of Visit Kits used for Urine Collection

Urine collection hats and jugs will be provided in bulk for distribution at visits screening, 6 months, and 18 months. Labels will be sent separately for each visit.

Supplies

6 x 8 mL plastic freezing vial (yellow cap)

Preparing the Tube and Vial Labels

1. Labels are provided for all tubes and vials. Blank specimen identification labels are provided for urine and bloods at screening visits. For CLCS and BBI specimens, labels will be pre-printed with participant's identification number for 6 month and 18 month visits and will be

sent to the clinical sites via UPS once all patients for that cohort are randomized. For CDC specimens, labels are provided by CDC.

2. At screening visits, for all CLCS and BBI labels: Record the subject's unique 10-digit identification code. Record the draw date of the visit or urine collection start date.
3. CDC Labels: You will be provided with a set of 6 preprinted labels per participant per visit. The ID number consists of a 4-digit prefix, followed by a one or two digit suffix. The prefix is participant specific; the suffix refers to the visit (5 = baseline, 8 = 6 month, 10 = 18 month). *The prefix does not match, nor should it be confused with, the participant's PREMIER ID number.* For eligible participants, one label should be placed on the 7ml hemogard SST vacutainer tube for processing. One label should be placed on each of the CDC cryovials. Record the participant's PREMIER ID on the label, as well as the draw date. The labels should be placed on the cryovial so that the bar-code label is horizontal, or "stair step", (i.e. when the vial is standing upright the bar-code lines will run horizontal (side-to-side)). The vials cannot be read if the barcode is placed on the vial in a different manner from what is noted above. Place one of the extra labels on the Form 77 in the box marked "Affix CDC label". **It is vital that the label placed on the particpant's Form #77 match the label on their cryovials. Failure to do this will result in the specimen being discarded for analysis.** Note: If a label becomes unusable during processing, affix one of the extra labels (with the appropriate visit number) to the cryovial.
4. At each intervention visit, all information will be pre-printed except for the draw date, which is recorded at the time of the visit.
5. Affix the completed labels to the appropriate tubes found in the kit before draw. Position the labels on the freezing vials over the white patch allowing the volume markings to remain visible.

   Note: It is imperative that all tubes are labeled correctly and completely, and that the writing be legible.

In addition to blood chemistries being measured at other external laboratories, serum levels of fat-soluble vitamins (vitamins A/E/carotenes/retinyl esters) and folate and vitamin B12 will be measured by the NHANES Laboratory at the Centers for Disease Control and Prevention. The procedures outlined below apply to specimen collection and processing for these specimens in the study clinics. It will be very important to assure that continuity of all techniques is maintained throughout the study duration, to minimize variability. This section provides all necessary information for correct collection, processing, and shipment of the study blood specimens for analysis, as well as a summary of procedures used by the NHANES Laboratory when the specimens are received at CDC.

Venipuncture blood samples will be collected by the clinic on each study participant. Subjects must have fasted 12 hours prior to blood collection, with only water allowed. Fasting is <u>required</u> for baseline samples. If the subject has not been fasting, the baseline blood draw must be rescheduled. At follow-up visits, if the participant is not fasting, the sample may be drawn. In this case, note on the form whether fasting time is sufficient. Processed serum samples will be

sent to the Centers for Disease Control and Prevention (CDC) for analysis and storage of any residual specimens.

Do not use the CDC-supplied materials for collecting or processing blood for any other study tests; they have been pre-screened for background contamination and it is imperative to keep them as clean as possible.

Preparing the 24-hour Urine Collection Labels

Four types of labels will be provided to place on each urine collection jug:
1. Collection instruction labels
2. Specimen identification and start/stop labels
3. Estimated spills labels
4. Collection procedure verification labels

Place all four labels on each urine collection jug prior to handing out to patients. The information on these labels is critical for proper collection documentation. Verify that all labels are properly completed when the jug is returned. If the patient requires more than one jug for collection, only one set of labels is required.

Preparing Forms 20, 21, and 77

1. Use one copy of each form and its worksheet per subject per visit. Fill out the top of each form (ID and Visit) and the top of each worksheet (ID) prior to the visit.
2. The remainder of each form will be completed at the visit.

Preparing the Storage/Shipping Supplies

1. A -70C freezer must be available for storing samples after collection and processing. Specimens will be shipped by Federal Express to the CLCS and BBI three times during each cohort. The screening shipment will go out after randomization and the intervention shipments will go out at the end of the 6 month and 18 month periods. Contact the laboratory and the repository prior to shipping.
2. You will need to store the specimens in boxes in the freezer until you are ready to send a shipment to CLCS or to storage. Complete the Freezing Log forms (Forms #328, 329, 330) when collecting the sample in order to record which sample is going into the slots in the freezer boxes. If you use freezer racks, create a site-specific Freezer Log form to track the locations of specimens. These forms are for internal use only. They will not be entered into the data entry system. See directions below for shipping the specimens.

At the Visit:

General Instructions

Treat all materials that have been in contact with blood or urine as potentially infectious. Dispose of these materials, including needles, by approved procedures for the individual site. Wear gloves to minimize the transmission of infection. Observe universal precautions when handling potentially infectious material.

Collection of Blood Samples

A fasting blood must be collected between SV2 and randomization, and at the 6 month and 18 month visit.

Subjects must have fasted 12 hours prior to blood collection, with only water allowed. If the subject has not been fasting, the visit must be rescheduled.

Due to the sensitivity involved in specific testing, standardization of specimen collection is imperative. The subject MUST be seated for at least 10 minutes prior to specimen collection. A tourniquet may be used for no longer than two minutes. Deviation from this standardized sample collection protocol will cause significant variability in assay results. Be consistent from visit to visit.

1. Clean with an alcohol pad, then draw blood from the crook of the arm, generally from the antecubital vein. Fully fill all tubes.
2. Draw the two 10-mL (red/gray top) SST serum tubes before the two 10-mL (purple top) EDTA plasma tubes. Non-additive tubes are drawn before additive tubes to avoid additive contamination of the non-additive tube. Cross-contamination between different additive tubes can also occur, making test results erroneous.
3. Thoroughly mix all tubes immediately after collection by gently inverting the tubes at least five times. *Do not shake*.
4. Remove the needle and apply pressure to the venipuncture site. Cover with an adhesive strip when the blood has stopped flowing.

The Central Lab Collection Form - Bloods (Form #21) is used for processing the fasting blood samples.

Preparation and Blood Collection for Folate, Carotenoids and Vitamin B-12

Summary

Collect and completely fill a 7-mL SST (“tiger-top”) Vacutainer [NO anticoagulant] from each study participant.

Blood Collection

Blood should be drawn from an antecubital vein or from some other convenient arm vein. Apply the tourniquet to locate the vein, then release it while the venipuncture site is being cleaned. Swab the venipuncture site with alcohol and allow it to dry. Reapply the tourniquet, reconfirm the vein location, and perform the venipuncture, using either a 21- to 23-gauge butterfly needle or a 21- to 23-gauge multi-sample Vacutainer needle. (Use of the butterfly needle will make tube changing easier since the needle can be taped in place.) Care should be taken to avoid protracted probing for vein location. Release the tourniquet before the needle is removed from vein. Prolonged application of the tourniquet should be avoided to minimize hemoconcentration.

Collect blood using a Vacutainer system following the instructions supplied with the tubes. (Training tapes are available from manufacturer, Becton-Dickinson, Rutherford, NJ.) The butterfly needles come complete with tubing and Luer adapters which fit into the Vacutainer holders, thus enabling the needle to be taped down to minimize movement while both hands may be used to change Vacutainers. Introduce the butterfly needle into the vein and fill the Vacutainers as completely as possible, collecting any other tubes with anticoagulant first, then the SST tube.

Use a dry gauze pad to apply pressure when removing the needle since a wet pad could result in fluid being drawn into the Vacutainer. After removing the needle, apply pressure firmly to the puncture site with the subject's arm held straight, rather than with the elbow bent, for at least 5 minutes to avoid hematoma formation. Re-examine the puncture site to verify that any residual bleeding has ceased, then apply a bandage as a precaution. Dispose of all needles and contaminated wastes properly in the biosafety container.

Make sure that each Vacutainer is clearly labeled with the subject’s ID number, using the provided labels. Apply a study label for each page of the participant’s paperwork as well.

<u>Offsite blood draws</u>

Refer to procedures outlined in Chapter 27, Offsite Data Collection Visits, for additional information regarding transporting specimens from offsite locations.

Safety Note

CDC recommends, as good laboratory practice that all blood specimens, used needles, etc., should be treated as though they were infectious for HIV and hepatitis B virus. All used needles and lancets should be placed in puncture-resistant containers; then, along with used gauze, Vacutainers, pipets, vials, Hemocue cuvettes, plastic-backed “diapers”, etc., they should be autoclaved prior to final disposal. Use of disposable gloves when collecting and processing blood is also required. (See CDC recommendations for preventing transmission of infection with human HTLV III/LAV in the workplace. MMWR 37:377-388, 1988).

Collection of Urine Sample

Between SV2 and randomization, and at the 6-month and 18-month visit, instruct the participant to collect a 24-hour urine specimen (see appendix A for sample instructions for participants). 24-hour urine collection should not be done during menstruation. Schedule urine collection to avoid collections during this time.

In order to maximize quality control for urine collections, the collections should ideally begin on Monday through Thursday when the participants come in to pick up their collection materials, and participants should be instructed to return the collections the next day. This enhances the likelihood that the initial voiding to start the interval is discarded and that a final voiding is obtained at the end of the collection interval. It should also maximize the likelihood that the collection duration falls within the allowable limits (22-26 hours). Incentives might be useful to encourage collection during the week. If, in the opinion of clinic staff, the participant is unlikely to comply with the collection regimen due to this weekday collection, the participant may be allowed to collect the specimen over the weekend. In this case it is still preferable to either begin or end the collection in the clinic, so that at least some level of quality assurance is achieved.

1. Distribute the 24-hour container and instructions to the participant and review the instructions with the participant. The instructions are included in Appendix A below.
2. Make sure that all four information labels are affixed to the collection jug and that it is filled out with the appropriate identifying information. If the subject has a high urine output, two jugs may be required.
3. If the specimen is to be returned the next day, have the participant start the collection before leaving the clinic (i.e., void the bladder into the toilet). Inform the participant to bring the container back within 24 hours of collection. Specimens should be refrigerated or kept in a cool place during collection. The instructions for processing the specimen should be followed no matter when the specimen is returned.
4. Take the 24-hour urine container from the participant, check to make sure that the labels on the tab attached to the jug are filled out correctly and completely, and verify that the ID listed on the label matches that of the participant. Also confirm that the participant: voided her bladder at the start of collection and did not save the specimen, collected a final voiding at the end of the collection period, and returned the specimen within 24 hours of the final voiding.

The specimen is considered to be inadequate if any of the following are true.

- The total duration of the collection is less than 22 hours or greater than 26 hours
- The collection period did not start with an initial, discarded voiding
- More than one voiding (including the final voiding) was missed
- The total volume of the sample is less than 500 cc
- The urine is collected during menstruation

If the specimen is inadequate, or if the participant failed to bring it in, a second specimen must be obtained. Give the participant a new set of collection materials, attach and fill out the labels

correctly. Save an aliquot from the original sample as a backup in case the participant is not able to provide an adequate sample, and note on the label that the sample was inadequate.

If the participant does not bring a repeat specimen, process the aliquot from the original (inadequate) sample in its stead, and note on the shipping label that the sample was inadequate and why. If both the samples are inadequate, send the better of the two samples.

Assuming that the participant does bring in a specimen, either immediately take it to the clinic's lab area for processing or place it in a refrigerator until it can be processed. Avoid leaving the specimen at room temperature for any longer than is necessary. In instances where these procedures weren't followed, specimens may be stored up to two days at room temperatures without affecting analyses. If stored for more than two days at room temperature, the specimen is unusable.

The Central Lab Collection Form - 24-hour urine (Form #20) is used for processing the 24-hour urine sample.

After the Visit

Process and Store Serum Specimens

1. Allow the 2 x 10 mL SST tubes (red/gray top) to clot for 30-60 minutes at room temperature in an upright position. Verify that the specimen is fully clotted.
2. Centrifuge the clotted tubes for 15 minutes at 1,500 x g. After centrifugation, check the SST tubes for a complete gel barrier between the serum and the cells. Re-centrifuge if the barrier is incomplete or if red cells are seen above the barrier.
3. Pour the serum from the SST tubes into the 13 mL pooling vial. Cap the pooling vial and gently invert several times to obtain a homogeneous specimen.
4. Using a transfer pipette, transfer 1 mL of serum from the 13 mL pooling vial into 3 x 2 mL freezing vials with red caps, labeled "Storage Serum" and 3mL or the remaining serum into a 1 x 8 mL freezing vial with red cap labeled for "CLCS Serum." A minimum of 3 mL is required for analysis.
5. Fasten the appropriately colored caps tightly and immediately place the vials in freezer racks at -70°C. As the samples are put into the box or rack in the freezer, you can use the Central Lab Freezer Log – Blood and Urine Samples (#328), and the Storage Lab Freezer Log – Blood Samples (#330) to help keep track of specimen locations. Use the log to note the box or rack slot number, participant ID, visit, collection date, sample type (e.g., plasma, serum) and any comments about the particular sample. These forms are for internal use only. They will not be entered.
7. Fill out the worksheet for the Central Lab Collection Form- Fasting Blood (Form #21)
8. If a repeat draw is necessary, repeat the steps above.
9. After any repeat draws for this participant are complete, use the worksheet to complete Form #21

Process and Store EDTA Plasma

1. Centrifuge the 2 x 10 mL (purple top) EDTA tubes without delay at room temperature. Centrifuge at >1,500 x g for 15 minutes to remove blood cells. No red cells should be present in the plasma or along the sides of the tubes.
2. Using a transfer pipette, transfer the plasma from both tubes into the 13 mL plastic pooling vial. Cap the pooling vial and invert several times to obtain a homogeneous specimen.
3. Using transfer pipettes, transfer 1 mL of the plasma from the pooling vial into 3 x 2 mL freezing vials (clear cap), labeled "Storage Plasma." Transfer the remaining plasma into the 1 x 8 mL freezing vial (purple cap), labeled "CLCS Plasma." A minimum of 1 mL is required for analysis.
4. At the screening visit only: Save the EDTA tubes that contain the cell pellet for the buffy coat. The buffy coat is the whitish layer of cells overlaying the packed red cells remaining in the EDTA tubes after the plasma is removed. Collect the buffy coats from both EDTA tubes and transfer into the 2 mL freezing vial with a purple cap labeled for "Buffy Coat."
5. Fasten the appropriately colored caps tightly and immediately place the vials in freezer racks at -70°C. As the samples are put into the box or rack in the freezer, you can use the Central Lab Freezer Log – Blood and Urine Samples (#328), and the Storage Lab Freezer Log – Blood Samples (#330) to help keep track of specimen locations. Use the log to note the box or rack slot number, participant ID, visit, collection date, sample type (e.g., plasma, serum) and any comments about the particular sample. These forms are for internal use only. They will not be entered.
6. Fill out the worksheet for the Central Lab Collection Form- Fasting Blood (Form #21).
7. If a repeat draw is necessary, repeat the steps above.
8. After any repeat draws for this participant are complete, use the worksheet to complete Form #21.

Preparing Serum for Folate, Carotenoids and Vitamin B-12

Fasting bloods are critical to an accurate evaluation of vitamins, particularly the fat soluble vitamins. Fasting for these blood draws is required at baseline. In follow-up every effort to collect fasting blood should be made. If fasting blood cannot be obtained, non-fasting blood should be collected and appropriately flagged on Form #77.

Avoid exposing these samples to light for any length of time. While it is not necessary to use amber tubes or to wrap the tubes in foil, do not process in front of a window. If transporting samples from a collection site to another location for processing or storage, enclose the tubes in a box or other light-protective container.

After the blood specimens have been drawn, allow the filled red-top or SST Vacutainers to remain at room temperature for 30-45 minutes **but no more than one hour** for complete blood coagulation. Centrifuge the SST tubes for 10-15 minutes at 2400-2800 RPM (1500 X G for most counter-top centrifuges, with swinging-bucket rotors). Do not open and "rim" tubes prior to centrifugation; this may introduce contamination. Be sure to use balance tubes in the centrifuge

if necessary. The time required for centrifugation is a convenient time to prepare the remaining supplies for specimen processing, to label serum vials, and to create a specimen list.

Carefully open each centrifuged tube away from your face, following Universal precautions to minimize aerosol formation. Decant half of the serum into each of the CDC cryovials. A minimum of 1 ml of serum is needed for each vial. Be sure that each vial is correctly labeled with the study participant's ID and test name.

Place the filled cryovials for each subject in the white storage boxes to keep them upright during shipment. Start on the top left corner of the box (where the dot is) and place the samples as follows to have 4 sets of samples per row:

> patient 1 vial 1, patient 1 vial 2, patient 2 vial 1, patient 2 vial 2, patient 3 vial 1, patient 3 vial 2, patient 4 vial 1, patient 4 vial 2, empty space.

Repeat this process with each row to the bottom of the box. Check off the spaces the transmittal sheets so that we will know that you successfully processed these vials in case of any discrepancies in shipment.

PREMIER Study samples will be collected at baseline, 6-month, and 18-month intervals. Since it may take several months for each clinic to collect their samples, the white storage boxes can be accumulated, stored at < -70 EC, and shipped to CDC on a monthly basis until that interval's collection is complete. We will send at least 5 boxes to each clinic. (Each box holds 9 rows x 4 patient vial sets, or samples form 36 patients.)

Process and Store Urine

1. Record the sample identification, dates and times on the Central Lab Collection Form- 24-hour Urine (Form #20).
2. Invert the sample container at least eight times to ensure a uniform sample.
3. Measure the total urine volume (use a graduated cylinder). Note the volume on Form #20.
4. Label and prepare 6 x 8 mL freezing vials (yellow cap) as follows:
   Tubes 1, 2, and 3: Add nothing to the vials labeled 'NO HCl".
   Tubes 4, 5, and 6: Add 2 drops of 6 N HCl to the vials labeled 'With HCl'.
5. Add 5 mL of well-mixed urine to tubes 1-6, using a graduated pipette. Cap securely. Invert to mix.
6. Fasten the yellow caps tightly and immediately place the vials in freezer boxes or racks (in an upright position) at -70C. As the samples are put into the box or rack in the freezer, you can use the Central Lab Freezer Log – Blood and Urine Specimens (#328), and the Storage Lab Freezer Log – Urine Samples (#329) to help keep track of specimen locations. Use the log to note the box or rack slot number, participant ID, visit, collection date, sample type (e.g., plasma, serum) and any comments about the particular sample. These forms are for internal use only. They will not be entered.

7. The remaining urine may be discarded. Be sure to use distilled/de-ionized water to rinse the graduated cylinders between samples to avoid cross-contaminating the specimen.
8. Fill out the worksheet for the Central Lab Collection Form- 24-hour Urine (Form #20).
9. If a repeat collection is necessary, repeat the steps above.
10. After any repeat collections for this participant are complete, use the worksheet to complete Form #20.

Complete Collection Forms

Once specimen processing has been completed, transfer the data from the worksheets for the Central Lab Collection Forms (#20, #21, and #77) to the first page of each form. Send the forms to the data entry technician to be entered.

Lab QC

To measure quality control and assay variability at the central lab, sites will be sending additional blinded specimens along with our regular shipments of participant specimens. The data entry system will print out reports for each participant for whom we will be sending a blinded specimen. Follow the instructions on the report to create the appropriate duplicate sample.

These duplicate samples are sent to the lab to verify the accuracy of their test results. Duplicate samples will be created in such a way that the central lab cannot readily identify them. This means that each sample has a fake ID, collection date, collection times, and other information. Duplicate specimens are obtained only during screening.

Form 66 will print out for randomly selected SV3 eligible participants when the SV3 visit form is entered (check printer). Once it has printed, check to see if the lab samples have already been collected. Most lab specimens are collected after SV3, but if this participant has already done their collection, just check “Yes” for the first question on the form. For forms where the first answer is “No," prepare for the duplicate collection by doing each of the items on the checklist. Refer to Form #66 coding instructions for more details.

Enter Form #66. Store the duplicate specimens in the same manner as the original specimens. When it comes time to ship lab specimens, the duplicates will show up on the packing and shipping logs with dummy ID numbers, just as if they were real participants. If the participant from whom the duplicate was collected is not randomized, you will be prompted to discard both their original and duplicate samples after the randomization period is over. (Central Lab Samples to Discard: LAB10 Report).

The coordinating center recognizes that creating the duplicates correctly is a difficult process. Please contact the Data Manager at the Coordinating Center if you have any questions or problems, or if there is any way the Coordinating Center can help smooth this process.

Shipping specimens to the central lab and storage lab

Data Entry/Data Management

In order to be able to send the shipment to CLCS or to BBI, you must send the completed Forms 20 and 21 to the data entry technician to be entered. When you are ready to ship, print out the Central Lab Data Completeness Report (LAB05) from the PREMIER Lab Tracking System to see if there are any additional forms you need to enter. All Central Lab Collection forms for a particular visit should be entered before preparing boxes for shipment.

Packing Boxes for Shipping

1. The central lab and storage lab will provide 2" and 3" cardboard freezer storage boxes.
2. To simplify the process of shipping specimens, sort the specimens in freezer into samples going to CLCS (bloods and urines can go in same box) and samples going to BBI (bloods and urines in separate boxes). Within these three groups, sort by ID and collection date. Specimens can be stored in the shipping boxes, or in racks.
3. The PREMIER Lab Tracking System is used to prepare the samples for shipment. Be sure to read the users manual carefully before beginning the shipment process.
4. Open the PREMIER Lab Tracking Management System.
5. Create a Box: The first step in Lab Tracking is to create a box for CLCS or BBI. You will only be able to work on one box type at a time. The system will search for all your entered Central Lab Collection forms. It will come back and tell you if you do not have enough samples to fill a box. You can then choose to prepare that box (and ship it only partially full) or not. The system will then automatically print out a working draft of the selected shipping log and visual map for you to start packaging the specimens. The visual map is a map of the slots for the particular type of box you will use. It will fill the slots starting from the bottom left hand corner with the participants who have completed Central Lab Collection forms in the system. The shipping log will have the same information that is on the visual map plus space to write in the shipping condition.
6. Prepare a box: Use the working draft of the visual map to fill the slots of the shipping box. Due to the space required by caps, the 3" boxes will hold 36 instead of 49 vials. The fourth position in each row and the entire fourth row must be left empty for the vials to fit. The starting location for filling these boxes is the front, left corner of the box, moving to the right, then to the back as each row fills. Specimens are sorted within the box so each participant's specimens are grouped together. Specimens for a single participant will not be spanned across two boxes, so some slots in a box may not be filled.
7. Edit Specimen Shipment Conditions: If any specimens that have been lost, broken, lost labels or become unusable for some other reason, (1) record the condition of the specimen in the shipping condition column of the shipping log, (2) leave that slot in the box empty. If there are any other problems with the specimens (i.e., hemolyzed) and you still plan on shipping that specimen, record the problem with the specimen in the shipping condition column of the shipping log.

8. Finalize a box: After all the specimens have been put in the box and the shipping conditions have been recorded. Note: the default shipping condition is "good", you will only need to note any conditions that are not "good". Go back into the Lab Tracking system and select a box to finalize. You will need to enter the following: Box preparer, prepared date, and any comments. Shipping conditions should have been edited prior to this step. Note: once you finalize a box, you will not be able to modify the data pertaining to that box.

Shipping Specimens

1. Shipping will occur three times during a cohort. The first shipment will be sent to CLCS and BBI following randomization, a second shipment will be sent at the end of the 6-month visits, and a third shipment will be sent at the end of the 18-month visits. Contact the lab and the repository before shipping. You will need to tell them the shipment date and the UPS/FedEx tracking number. An analysis date will be set at CLCS prior to the end of each cohort. Failure of the specimens to arrive at CLCS prior to this date will result in a delay in processing.
2. Sending a box: When all boxes are packed and ready to be sent, you will need to enter the actual sent date in the Lab Tracking system. Select a box to send in the system. You will be required to enter the sent date and you can add any additional comments if needed. After entry of the sent date, the system will automatically print out a final shipping log and visual map for you to include with the shipment.
3. When the shipping box is packed, make three copies of the shipping log and two copies of the visual map. Keep one copy of each on file at the site, send one copy of each with the specimens to the relevant laboratory, and send one copy of the shipping log only to the CC. Do not send the working drafts.
4. Ship specimens to CLCS and BBI in the large shipping container provided. Obtain sufficient dry ice to fill the cooler. Note: Delay in adding dry ice to the specimens after removal from the freezer will allow specimens to thaw. Insufficient dry ice during shipment will do the same. Any degree of thawing before analysis will damage the specimens and compromise assay results. Please see the packing/shipping instructions provided by the labs. They will send these instructions with the shipping containers. The CLCS will confirm receipt of shipment with the CC.
5. Notify CLCS and BBI before sending each shipment.
   CLCS: Phone: (314) 362-3522 Fax: (314) 362-4782
   BBI: Fax: (301) 208-8829
6. Specimens must be shipped by Federal Express to:
   Dave Gibson
   Core Laboratory for Clinical Studies
   Lipid Research
   4940 Parkview Place
   St. Louis, MO 63110
   Phone: (314) 747-1127
   -or-

Carla Hansen
BBI - Biotech Research Laboratories
217 Perry Parkway
Gaithersburg, MD 20877
Fax: (301) 208-8829

7. If you have any specimens left that have not been assigned to a box and shipped, print out the following reports from the Lab Tracking system: Central Lab Data Completeness (LAB05) and Central Lab Samples to Discard (LAB06) to verify the remaining samples. The first report will show the samples we are expecting to send and the second will show those samples of non-randomized participants you will need to discard. If there are any additional remaining specimens that you are unable to deal with using the above reports, please contact the Data Manager at the CC.

Shipping Specimens for Folate, Carotenoids and Vitamin B-12

Specimen shippers will be supplied by CDC, and the outside covers will have been covered with clear plastic tape to facilitate the removal of shipping labels. Periodically, we will refurbish these shippers with new outside covers. Fill out the shipping manifest list supplied by CDC itemizing participant's identification numbers, date of collection, clinic name and location, and mailing date for each shipment. Add any pertinent comments regarding condition of specimens such as "inadequate blood draw," "serum specimen hemolyzed," etc. Include one copy of the shipping manifest list with the shipper under the outer lid, and if possible, fax a copy to CDC (770-488-4609) to enable us to track shipments (*please be sure to include the FedEx or UPS shipment number on this copy, **as well as the Premier Study Tracking #2000-0030***). Retain a third copy in the clinic for your records. Arrange for shipment by Federal Express or other express courier. Centers are responsible for shipping costs.

When packing the shipment, please follow these instructions:

(1) Put a layer of several paper towels or sheets of newspaper in bottom of the Styrofoam shipper to act as cushioning. Place at least 10-12, preferably 15, pounds of dry ice in the bottom of the shipper. Do not stint on the dry ice or your specimens could arrive thawed if the shipment is delayed. Chunks or pellets of dry ice are easier to handle than slabs, but do tend to volatilize away more quickly. Add another layer of paper. (Dry ice should never come into direct contact with the plastic bags.)

(2) Enclose each white box in a large ziplock bag to contain its contents in case of breakage.

(3) Place the ziplock bag containing the white cardboard box, "right-side up", on top of the paper towels. Fill the remaining space with "bubble"wrap or paper towels or wadded up newspaper to prevent to specimens and dry ice from moving around inside the shipper. The empty white boxes and ziplock bags will be returned to the

clinics after each shipment.

(4) Make sure the Styrofoam inner lid is completely closed to preserve cold temperature.

(5) Place the shipping list on top of the Styrofoam lid. Secure the outer cardboard lid of the shipper firmly with clear or nylon reinforced strapping tape, and attach the Federal Express label. Excessive amounts of tape are not necessary, since the shippers will be returned to each clinic after each shipment. The tops of each new shipper will be covered with the clear tape to make removal of old labels easier.

Send all shipments to CDC by an overnight express courier on Monday, Tuesday, or Wednesday, and arrange shipment time so that the shipment does not arrive on a weekend or a holiday without advance notice. Specimens should arrive at CDC within 72 hours of shipment.

Address shippers as follows:

Mr. Charles Dodson
Centers for Disease Control and Prevention
4770 Buford Highway
Bldg. 17 Loading Dock
Atlanta, GA 30341

Include your clinic address and telephone number on the shipping label and ensure the **Premier Study Tracking # 2000-0030 is noted on the label.** This tracking # is used by CDC to keep track of different study samples arriving at CDC and for linking each study sample to it's relevant electronic data file.

Your primary contact persons at CDC for specimens and shipping questions are Charles Dodson and Dan L. Huff. Their contact details are:

Charles Dodson at (770) 488-4305 or fax (770) 488-4541 or e-mail WCD1@CDC.GOV
Dan L. Huff at (770) 488-7932 or fax (770)488-4609 or e-mail dlh1@cdc.gov

Notify them when your shipment is being sent to CDC as they need to know when to expect them so it will not be lost /misplaced within CDC.

E-mails should go to both Charles Dodson and Dan L. Huff incase one is away. Be sure to mention the Premier Study and Premier Study Tracking # 2000-0030 in the subject line of any e-mails sent to CDC.

Central Laboratory Procedures

Shipper Receipt at CDC

Once a shipper arrives at CDC, it will be logged in by the receiving clerk. Specimens will be removed and frozen for short-term storage (several days at most). White storage boxes and new ziplock bags will be replaced in the shipper. Excess labels will be removed carefully, and the shipper will be resealed and returned by surface mail to the originating clinic for reuse. Periodically, new outer cartons will be provided for the Styrofoam inner shells.

All excess serum will be stored at -70 EC until study completion, at which time NHLBI may decide to archive these specimens permanently elsewhere.

Reporting of Results

Quality assurance is an important component of reporting of results. If specimens arrive at the CLCS that cannot be analyzed (e.g., not labeled, thawed, insufficient quantity, etc.), the laboratory will notify the clinical site and coordinating center.

The clinical site will be notified of all alert laboratory values (glucose <40 or >400, and total triglycerides >900) as soon as results are available. Alert values are listed in Appendix B.

Prior to release of all results, the values are verified as outlined below. Reference ranges are listed in Appendix B.

- Extreme values are flagged. Assays are repeated and results are verified.
- Delta Checks are reviewed for previous visit comparison. Discrepancies are investigated.

Electronic Data will be transmitted to the sponsor after randomization and after the 6-month and 18-month visits for each cohort.

Appendix A: 24-Hour Urine Instructions

Instructions for Standard Weekday Collection

To collect a 24-hour urine specimen, you will need a plastic sample container (women may also want to use a collection device referred to as a hat). The container should be labeled with your study identification number, the date and time you begin the urine collection and the date and time you complete the collection. It is important to collect all of the urine you pass during the 24-hour collection. However, if you do forget and miss a collection, it is equally important that you indicate how many voidings were missed on the tag at the end of the collection.

Women should use the hat to help collect the sample, place it under the toilet seat, urinate into the hat, and then carefully empty the contents of the hat into the jug. Otherwise, urinate directly into the jug. In the event of a spill, please estimate the amount spilled; write the amount on the recording tag (e.g., "1 tsp spilled"). If you miss a sample, record this on the tag in the place provided.

You will begin your urine collection at the clinic. When you arrive at the clinic, you should void but do not collect this urine. This is the start of your collection period. Beginning with the second urination of the day, collect all urine for the next 24 hours from the time of the discarded urine. Every time you have to urinate, collect the entire sample in the container. For example, the last sample collected should be voided 24 hours after the clinic urination (the times on the recording tag might be 4:00 p.m. start time and 4:00 p.m. stop time, for example) and should also go into the container. Record the date and time of your final urination on the tag of your container. Store the container in a refrigerator or a cooler between voids if possible. Bring your sample into the center as soon as possible after collection is complete.

Special Instructions for Weekend Collection

Weekend collections should only be done if it is not possible to do the collection on a weekday. Quality control is much improved if the collection starts and ends with a void at the clinic.

Begin the urine collection in the morning. Discard the first void of the day, but mark this as the start time. Write the start date and time on the jug. Beginning with the second urination of the day, collect all urine for the next 24 hours from the time of the discarded urine. For example, if the first void (which is discarded) was at 7:30 am on Sunday, the final void (which is collected) should be at or very close to 7:30 am on Monday.

Every time you have to urinate, collect the entire sample in the container. Record the date and time of your final urination on the tag of your container. Store the container in a refrigerator or a cooler between voids if possible. If more than 24 hours will elapse between the start of the collection, and bringing the jug into the clinic, the jug ***must*** be refrigerated. Bring your sample into the clinic as soon as possible after collection is complete.

Appendix B: Reference Ranges and Alert Values

Lipid Profile

Analyte	Units	Reference Range		Alert Level *
Total Triglycerides	mg/dL	Desirable: Borderline High: High: Very High:	≤ 200 201-399 400-1000 >1000	>900
Total Cholesterol	mg/dL	Desirable: Borderline High Risk: High Risk:	< 200 200-239 ≥ 240	N/A
LDL Cholesterol	mg/dL	Desirable: Borderline High Risk: High Risk:	< 130 130-159 ≥ 160	≥190
HDL Cholesterol	mg/dL	Desirable: High Risk:	≥ 35 < 35	N/A

Urine Chemistry

Analyte	Units	Reference Range		Alert Level*
Urine Sodium	mmol/24 hr	40-220		N/A
Urine Potassium	mmol/24 hr	25-125		N/A
Urine Phosphorous	g/24 hr	0.4-1.3		N/A
Urine Creatinine	mg/24 hr	Male 800-1800	Female 600-1600	N/A
Urine Urea Nitrogen	g/24 hr	12-20		N/A
Urine Volume	mL/24 hr	Male 800-1800	Female 600-1600	N/A

Chemistry and Special Chemistry

Analyte	Units	Reference Range	Alert Level*
Glucose, Fasting	mg/dL	65-110	>125 or <40
Homocysteine	µmol/L	6.0-16.0	N/A
Insulin, Fasting	µIU/mL	0-23	N/A

***Notify participant as soon as alert result comes to the attention of the clinical site.**

22. PHYSICAL ACTIVITY ASSESSMENT 4

Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- Intensity is determined by participant self-report, but final judgement rests with the interviewer. If there is any difficulty with participant's report of intensity for a particular activity, interviewer determines intensity using the Compendium.

22. Physical Activity Assessment

Acknowledgements

The 7-day Physical Activity Recall has been adapted form work done at San Diego State University (Project Grad, James Sallis, Ph.D., Principal Investigator) and the Cooper Institute for Aerobics Research (Project Active, Steven N. Blair, P.E.D., Principal Investigator) and the Activity Counseling Trial.

Introduction

The 7-Day Physical Activity Recall (PAR) interview technique is used to estimate an individual's average daily energy expenditure for the previous week. Based upon participant recalls, hours spent in sleep and in ***moderate, hard,*** and ***very hard*** intensity activities are determined. By mathematical difference, these data will then be used to estimate activities classified as ***light*** intensity. Total kilocalories can then be estimated from the number of hours engaged at the various levels of intensity. The purpose, therefore, is not to single out specific physical activities but to identify participation in activities at various levels of intensity. The interview looks at work-related activities, leisure-time activities, and sleep patterns. The purpose of this manual is to standardize the interview process and to increase agreement among interviewers.

A staff person's interview technique should limit bias (it should be objective), and should try to keep the interview from becoming tedious. To achieve these goals, an interviewer script is included in Appendix 1. Although the interviewer does not have to memorize this script, it should be followed very closely to reduce variability between and within interviewers. A major effort should be made by the person conducting the interview not to be judgmental of participant responses. There are no right or wrong answers to the interview. It is important to set a positive, non-threatening tone and to put the participant at ease at the beginning of the interview. It is also important to remember not to become sidetracked by the study participant. It may be difficult for participants to remember their past week's activity. Some may not try very hard, and others get bogged down in details. Interviewers should strive to achieve a happy medium by controlling the pace of the interview and avoiding extraneous talk. If participants are going into excessive detail, remind them that they need not account for every minute, but that an average or estimate is expected. For example, the interviewer might ask, "How much time in general?" or "about how long?"

It is important to remember that most participants spend a vast majority of their waking hours doing ***light*** activity**.** Many tiring and unpleasant household or occupational tasks do not have a very high energy cost. Clerks in a store, for example may be on their feet all day and may feel fatigued, but the energy cost is in the ***light*** category. An exception to this example would be time spent in stocking shelves, which probably would be classified as ***moderate*** activity. Also, for most occupational tasks that require at least moderate energy expenditure, it is important to accurately determine the actual time spent doing the activity. In the stocking clerk example,

even though a person might do that activity for an entire shift, it probably would not equal eight hours. You should try to subtract time spent on lunch, breaks, and the like.

Blinding

It is preferred that the PAR be administered by a blinded staff person. When this is not possible, the PAR may be administered by an unblinded staff person who is not doing intervention visits or taking outcome blood pressure measurements.

Interviewer Preparation Guidelines

The following points should be explained to each participant before actually beginning the physical activity interview. Reviewing the interviewer script provided in Appendix 1 will assist in communicating this information.

The participant is to think of physical activities during the past seven days. It is important to stress that this is a recall of actual activities for the past week, not a history of what they usually do.

Light activities, such as deskwork, standing, light housework, softball, archery, bowling, and the like (where there is little movement of large muscles) will not be considered during this interview. For the 7-day recall, we are interested in occupational, household, and sports activities that make you feel like you are working as hard or harder than when you are walking briskly (15-20 minutes per mile for most people).

Explain to the participant that he or she will be asked to categorize the intensity of the activity into one of three groups, ***moderate, hard*** or ***very hard***. Explain that the ***moderate*** category is similar to how one might feel while walking briskly and that the ***very hard*** category is similar to how one might feel when running. The ***hard*** category falls in between. In other words, if the activity in question seems harder than walking briskly but not as strenuous as running, place it in the ***hard*** category.

Prior to the interview it is a good idea to give examples and interact with the participant to allow feedback for a complete understanding of the types and intensities of activities that would fall into these categories. Laminated cards highlighting examples of each of the intensity categories are provided to each interviewer.

Prior to conducting the interview, the interviewer should be familiar with the energy cost of many common activities (see the Certification and Quality Control monitoring section in this chapter). Study personnel are urged to consult the reprint of Ainsworth, et al. (see Appendix) for a listing of these energy costs in METS (metabolic equivalents). Activity of 3-5 METS is considered moderate intensity activity. 5.1 - 6.9 METS is considered hard, and 7.0 or more METS is considered very hard.

Should any questions arise regarding administration of the PAR during the course of PREMIER, study personnel are requested to contact the Data Manager at the Coordinating Center for clarification and direction. All issues raised during the study are recorded in a log book for future reference.

Interview Protocol and Guidelines

Physical activity recall data for PREMIER is collected on pre-printed forms entered into the computer. Detailed information on participant interviewing can be found in the interviewer script (Appendices 1-3). Detailed information on completion of the pre-printed forms is found below.

Required materials

- 7-Day Physical Activity Recall Form (#18)

The complete instructions for completing the PAR form are included with the form (administration, coding, and review instructions). The following sections are an overview to the process, but the instructions included with the form contain more detail on some items and should also be reviewed.

Completing the introductory questions

The first page of the PAR Form (Form #18) contains two questions used by the computer system to identify the days of the week referenced in the worksheet. Please fill out the first question by identifying the day of the interview.

Then ask the participant to identify their weekend days and check them off under the second question. If the participant does not work or does not have a "weekend", do not check any of the items. If left blank, note this in the margin to show that the answer is not applicable rather than missing.

If a person has weekdays instead of weekends off from work—for example, Tuesday and Wednesday instead of Saturday and Sunday—ask the participant if they consider the weekdays they have off as their weekend. If they do not consider the days off as their weekend days, ask them which days are most like weekends. Some participants may only consider one day as their weekend day. Others may have three-day weekends. The point here is to determine the participant's non-work days, as they are likely to have a different routine than the workdays. Make sure to count the most appropriate days of the week, as indicated by the participant, as weekend days.

Use of the Worksheet

The PAR worksheet (page 2 of the PAR form) is used to help the interviewer summarize the physical activity reported by the study participant. The number of hours and minutes (__:__) that the participant reports having spent in moderate, hard, and very hard activities (as well as sleep time) are recorded on the Worksheet. These data are then entered and used to calculate an estimate of energy expenditure.

Establishing the days of the week

To aid the participant in recall, ask about each day in turn, starting with yesterday and working backwards. "Okay, today is Tuesday, yesterday was Monday." Also, make sure to label the worksheet (see below) with the appropriate days of the week

Do this by placing yesterday's day of the week in the blank below the column labeled "Yesterday". Then, working backwards with respect to the day of the week, write each of the past 6 days of the week in the appropriate space above the columns, ending with the last day of the recall week below the column labeled "One Week Ago". This makes logging the participant's activities much easier. Also, connecting activities to specific days of the week helps the participant to remember more.

Using the participant's answers to question 2 on page 1, identify their weekend days and mark them with a "W" above the column.

Sleep

The first item on the PAR Worksheet is an assessment of the participant's sleep times for the week. The goal in estimating the sleep pattern in the PAR is to get an estimate of an individual's hours spent in bed per night. Even if they claim not to have slept, if they were in a prone position, they used approximately the same number of kilocalories as sleep, so that time should be counted as "sleep".

The sleep time should be rounded to the nearest ¼ hour. For example, if the individual reported 20 minutes, round down to 15 minutes (:15). If they report 25 or 35 minutes, this would be rounded to 30 minutes (:30), if they have 40 or 50 minutes, round to 45 minutes (:45), and if they report between 55 and 05, round to the nearest hour (:00). Many people will get in bed and get out of bed at consistent hours on the weekdays. This should be determined as an initial step by asking the following:

"For the past 5 weeknights, did you usually get in bed and get out of bed at the same time, or did it vary each night?"

If the times vary most nights, go day by day, beginning with getting in bed last night and getting out of bed this morning (the day of the interview). Work your way back through the week

asking for the specific times they got in bed and got out of bed each night and day. Going backwards helps people remember by starting with the most recent timeframe.

If the times of getting in bed and getting out of bed are fairly constant during the weekdays, ask what time they got in bed and what time they got out of bed and record these numbers on the worksheet. Ask the participant if there were any unusual weekdays when they might have gotten in bed or out of bed earlier or later. Record any of these changes on the appropriate day.

Next, ask the participant about the past Saturday night getting up on Sunday and the last Friday night (or equivalent weekend days) getting up on Saturday. Record these numbers on the worksheet.

For example, if the interview takes place on a Tuesday, the first night of recorded sleep (working backwards from Tuesday) would be going to sleep Monday night and getting up on Tuesday morning the day of the interview. The total number of hours slept in this time frame would be recorded for Monday night (labeled "yesterday" on the Worksheet). The next night of sleep assessed would be Sunday night, getting up on Monday. This number would be entered into the Sunday column. Therefore, keep in mind that although the labeled column refers to that *day's* activities, it also refers to that *night's* sleep times.

Keep in mind that some people may nap during the day or fall asleep while reclined in a chair. This time should be added to the pertinent night's sleep time. To capture this information, the participant should be asked if they took any naps or laid down for any period during the last seven days. Interviewers should be particularly alert to this if there was a night of limited or no sleep time.

Activities during the day

Starting with yesterday and working backward, ask about activities during each day. Ask only about activities that are ***moderate***, (at least the intensity of brisk walking), ***hard*** (intensity between walking and running), and ***very hard*** (intensity of running).

Ask about activity during each segment of each day as a separate question. For example, "On Wednesday morning, from the time you got out of the bed until the time you had lunch, did you do any physical activity you would consider moderate, hard, or very hard?" Morning is generally considered from the time they wake up in the morning to the time they have lunch, afternoon is from lunch to dinner and evening is for dinner until the time one goes to bed. The previous question would then be repeated for the remaining segments of the day.

It will help recall significantly to have the participant remember what he or she did during the day in question. If the participant is having trouble remembering their activities during each segment of the day, ask the general question, "Do you remember what you did on (Tuesday)?" Once the participant starts remembering, switch back to the segments of the day as outlined above (i.e., morning, afternoon, evening).

The interview needs to be sensitive to walking. However, people walk many times during the day, and we will not count all of them. For example, we do not want them to add up each time they walk to the refrigerator. The general rule is that they should do 10 minutes in a given intensity category in a given segment of the day (e.g., morning, afternoon, evening) for it to count. The specific rule for walking is that you only count walking that is done at a brisk pace and for at least 10 minutes.

Some people will provide exact times (i.e., "I walked 3 miles in 45 minutes 35 seconds.") In these cases, round times to the nearest minute.

Frequency

Probe to determine if the amount of the activity the participant reports is per weekend, per week, or per day, etc. Someone may say, for example, "I did one hour of digging this past weekend" when what he or she meant is, "I did one hour of digging each of the two days this past weekend."

Some people have trouble recalling or pinpointing the moderate to very hard activities they have engaged in over the past seven days. In such cases, try to cue them by asking them general questions. For example, "How about any housework that made you feel similar to brisk walking?" "Did you take any walks?" How do you get to and from work?" "Did you do any vigorous home repair or gardening?"

Take a retrospective look back at each day by asking the respondent whether there is any activity they may have forgotten to mention.

Intensity

Make sure to emphasize the intensity guidelines. Use the list of activities in Appendix 5 to make a laminated card listing common activities and their intensity levels. If you are unsure of the strenuousness of an activity that a participant may have participated in, ask him to describe the physical effort involved. For example, what does the activity entail?

Walking and running provide good frames of reference for classifying activities. Everyone should be familiar with the relative intensity of brisk walking, which is about the midpoint of the moderate activity category. Therefore, if some other activity that the participant reports seems to be about as strenuous to the individual as walking briskly**,** then the activity should be coded as ***moderate*.** If the activity is of an intensity less than a brisk walk, it is considered a ***light*** activity and is not included in the worksheet.

Most running or jogging at any speed falls into the ***very hard*** category. If some activity seems about as strenuous to the individual as running, classify the activity as ***very hard.*** If the activity

in question seems harder than walking, but not as strenuous as running, place it in the ***hard*** category.

For most activities, the rate at which they are performed can make a huge difference in the energy cost. It is possible to play single tennis, for example, so as not to move around much and not expend much energy. Try to get some indication of how hard the participant is working at a particular task. Again, use comparisons to walking and running so the participant can rate how hard she did the activity.

Time

Some people have trouble quantifying the amount of time they spent doing moderate, hard, or very hard activities. In such cases, break down all of their activities into specific events and ask them how long they did each activity. Then sum up the amount of time relevant to each category. If the individual is having difficulty quantifying the amount of time engaged in a particular activity, suggest to the individual possible time frames such as 15 minutes, 30 minutes, 45 minutes, or an hour. However, it is not necessary to round participant answers to anything but the nearest minute.

The activity in question should be performed for at least 10 minutes during one segment of the day: morning, afternoon, or evening. For example, if their activities last at least 10 minutes in one intensity category (e.g., hard) for one segment of the day (e.g., Wednesday afternoon), the total time of those activities should be counted. If 10 minutes of activity is spread out over two or more segments of the day, it is not counted.

Be sure that the time reported for an activity was actually spent doing the activity. Being at the pool for 2 hours but only swimming for 15 minutes, for example, should be recorded as 15 minutes, not 2 hours. Working in the garden all day Saturday (8 hours) should mean actually working for 8 hours. Do not record the time spent on breaks, rest periods, meals, and the like.

Cells with no activities reported

For any day/time/intensity where no activities were reported, leave the cell blank. To remember that these were intentionally left blank, run an arrow through the cell(s) down to the end of the column or to the next cell with activity reported. See the sample included in the coding instructions for the PAR form for an example of a completed form.

Special Cases

If the last week was totally atypical--for example, in the hospital or in bed, or involving a family crisis, or a work crisis, or travel—it is permissible to go to the previous week for the survey. <u>Do not take this action lightly; use it only in unusual circumstances and notify the CC of the exception</u>.

Strength and Flexibility Exercises

Any reported strength and flexibility exercises performed for at least 10 minutes should be recorded on the worksheet if they are performed at the moderate, hard, or very hard intensity level as are any other physical activities. Usually, strength and flexibility exercises will be recorded as moderate physical activities, however, the interviewer should be confident that these activities are performed at the same intensity as going on a brisk walk. The classification can be verified by determining the time spent in the activity and the total number of exercises (i.e., number of sit-ups, push-ups, etc.) performed during that time period.

Participant review

At the end of each day of recall, the interviewer should ask the participant to take a retrospective look of the past week as well as at the end of each day to determine any activities that may have been overlooked.

Use cues as much as possible to aid in the participant's recall of the past week. For example, "Did you want to add any other household, occupational, or sports activities that you participated in the past week and that we have not talked about?" "Did you take any walks we have not already covered?" "Are there any activities that you are unsure about?" However, it is important that the interviewer administer these questions consistently to all participants.

After the participant has reviewed his answers, ask him the two questions at the bottom of the worksheet and record his answers.

Types of activity questions

Ask the participant to complete the questions about types of activity on pages 3 and 4 of the questionnaire, and the question about vigorous activity on page 4 of the questionnaire. Review the pages to be sure all items have been answered. Thank the participant for her time and participation. The interview is concluded.

Evaluation and review by the interviewer

The interviewer should fill out the interviewer evaluation section of the form once the worksheet and supplemental questions are completed. This subjective opinion of the interviewer is important to evaluate data quality.

Procedures for dealing with data from interviews determined to be invalid are handled on a case-by-case basis. Interviewers and/or clinic coordinators are requested to discuss such cases with the Data Manager at the Coordinating Center.

Prior to data entry, the interviewer should visually review each form and ensure the completeness and correctness of each entry. Questionable intensities of reported physical

activities (question #3 on the interviewer evaluation page) should be verified using the Compendium of Physical Activities or with the local master trainer or study master trainer.

Important procedures the interviewer often overlooks

Ask about each day in turn, starting with yesterday and working backwards. "Okay, today is Tuesday, yesterday was Monday." Also, make sure to label the worksheet with the appropriate days of the week. This makes logging the participant's activities much easier.

Connecting activities to specific days of the week aids the participant in recall of events. Before asking about activities, it might help to ask the participant what he or she did that day, in general. "Where did you go and what did you do on that day?" Again, this helps them recall activities specific to that day.

Ask separately about each segment of the day. "What activities did you do in the morning; in the afternoon; in the evening?" Again, this helps the participant to remember more clearly.

Several times during the interview, remind the participant to think about all physical activities including work, household, and leisure/sport activities.

Count walking that is done for at least 10 minutes continuously. However, for the activity to be counted, the walking must be done at a brisk pace.

The purpose of the PAR is to estimate energy expenditure, so an activity does not have to be continuous to be coded. If their activities add up to at least 10 minutes in one intensity category (e.g., hard) for one segment of the day (e.g., Wednesday afternoon), then that activity or those activities should be counted.

For example, consider 60 minutes of gardening, which included both digging and planting. If the participant alternately dug and stopped to plant in five-minute intervals, this activity would be recorded as 30 minutes of digging and would qualify as hard activity. If 10 minutes of activity is spread out over two or more segments of the day, it is not counted. For example, 5 minutes of walking in the morning, 5 minutes in the afternoon and 5 minutes in the evening do not qualify. This rule allows the interviewer to code sporadic activities, but it does not force one to code every single minute of activity during the day, which would be too time consuming.

At the end of the interview, ask the participant if he/she forgot any activities.

The interviewer should not guess what intensity an activity is. Have the participant classify all activities into intensity categories, using the rule: running is very hard, brisk walking is moderate, and hard is in between. If the participant is unable to determine the intensity, or the interviewer questions the accuracy of the intensity level reported by the participant, the interviewer refers to the Compendium to determine intensity. The Compendium in not used for every activity; only for those activities for which there is some difficulty with the participant's

report of intensity. The final judgement about intensity rests with the interviewer. Use the Compendium as a tool to help make these judgements.

Weekend days should be marked with a "W" above the column.

If the participant offers information about sexual activities, the interviewer should offer his or her thanks, but the activity should not be recorded. However, do not make a point with the participant that the activity won't be recorded.

Certification and Quality Control Monitoring

Initial Interviewer Certification

Prior to conducting physical activity recall interviews for PREMIER, relevant staff are required to be certified in the interview procedure. During initial training for PAR measurement, this certification requires the following steps:

a. A personal review of an ACT PAR audiotape containing sample 7-day PAR interviews.
b. Attendance in a three hour training session led by a qualified individual experienced in PAR administration. This session includes practice sessions in which the interviewer has the opportunity to administer at least two practice PAR interviews under the supervision of the instructor. The instructor provides appropriate feedback and guidance.
c. Personal review by qualified instructor.
d. Review by qualified instructor of two practice interviews recorded on audiotape.

Initial Certification During Course of Study

For those individuals unable to attend the initial PAR training sessions conducted at the Coordinating Center in June 1999 and those who join the study team while the study is occurring, opportunities at individual Clinical Centers are provided for PAR interviewer certification. There are four stages to this decentralized approach to certification:

a. A personal review of ACT PAR audiotape containing sample 7-day PAR interviews.
b. Attendance in a three hour training session led by a qualified individual experienced in PAR administration. This session includes practice sessions in which the interviewer has the opportunity for administering at least two practice PAR interviews under the supervision of the instructor. The instructor provides appropriate feedback and guidance.
c. Personal review by qualified instructor via telephone or audio tape. The interviewer conducts two practice physical activity interviews under supervision. Feedback is provided and, upon completion, the interviewer is certified.

Recertification and Monitoring

To minimize "interviewer drift", all certified PAR interviewers are monitored for quality control. Each interviewer is observed every 6 months by the local master trainer on two separate interviews and provided feedback where necessary. Local master trainers are observed by another local master trainer (if one exists) or by an experienced interviewer every 6 months as well. Local master trainers are re-certified annually at the clinical measures training session.

Appendix 1: Interviewer script

Note to the interviewer: This script is provided to help in the administration of the 7-Day Physical Activity Recall for PREMIER. While you do not need to memorize this script word for word, you should become familiar enough with it to be able to closely follow along. For the most part, this script only contains what you should say to the participant. Instructions in coding the information and recording it on the 7-Day Physical Activity Recall form are included in the coding instructions attached to the form. Interviewer Tips and Probing Tips are included at the end of this script.

Italicized instructions in parentheses are for the interviewer and are not part of the script to the participant.

(Complete the first question on page 1 and label worksheet with days of the week from yesterday to one week ago, prior to starting the detailed interview.)

(Page 1)

"Hi, *(participant's name)* . We're going to do a 7-day physical activity recall together. We'll go over the last seven days and what you actually did for physical activity or exercise during those days."

"To start off, what days of the week do you consider to be your weekend or non-work days? For most people this would be Saturday and Sunday but it may be different for you." *(Record answer under question 2)*

(Page 2)

"There are three intensity levels that we want to talk about. The first one is moderate intensity physical activity. Here are some examples of moderate intensity activities *(show laminated card).* These would all be about the same intensity as going on a brisk walk."

"The next level is hard intensity activity, and here are some examples of hard intensity activities *(show laminated card).* This would be activity that's a little harder than going on a brisk walk, but not quite as hard as running."

"The last intensity level is very hard intensity activity. Here are some examples of very hard intensity activities *(show laminated card).* These would all be about the same intensity as running."

"Remember, these are just examples, so some of the activities you do that are moderate, hard, or very hard may not be listed on these cards. If you have any questions about how to rate an activity just ask me. A lot of the activities people do are considered light intensity activities,

which are less than moderate intensity activities. You won't have to report these types of activities."

"We're also going to break the day up into 3 general time segments. Consider morning as the time after you get out of bed until the time you have lunch. Afternoon is the time after lunch, but before dinner, and evening is the time from dinner until the time you get in the bed. Remember, these are just general guidelines that work for most people."

"Let's talk now about your sleeping habits over the last seven days. On those weeknights did you get in bed and get out of bed at the same time or did it vary*?" (Remember for recording purposes, weeknights are the nights before a weekday. Example: if weekdays are Monday – Friday, the weeknights are Sunday – Thursday.)*

> Participant says "About the same every night." "OK, what time was it that you got in the bed? What time did you get out of the bed? Did you have any unusual weekdays when you got in bed or out of bed earlier or later? Let's go back to (most recent weekend night). What time did you get in bed on (most recent weekend night) night? What time did you get out of bed on (weekend morning)? How about on (next recent weekend night) ? What time did you get in bed? What time did you get out bed on (morning of next weekend night) ?"
>
> Participant says, "They vary." "OK, let's think back on last night getting up this morning. What time did you get in the bed last night? What time did you get out of the bed this morning? Let's think back on (night before last) what time was it that you got in the bed? What time did you get out of the bed (yesterday) morning? Repeat by going backwards through the last 7 nights."

"Did you take any naps or lay down for any period of time during the last 7 days?"

"Now we're going to talk about your moderate *(point to card),* hard *(point to card),* and very hard *(point to card)* activities for the last week."

Let's think back on yesterday, which was (yesterday). On yesterday morning, from the time you got out of bed until the time you had lunch, did you do anything you would consider moderate, hard or very hard*?"*

"How about yesterday afternoon, from the time you had lunch until the time you had dinner?"

"What about last evening, from the time you had dinner until the time you got in the bed. Anything moderate, hard, or very hard*?"*

(Continue working backward for each day of the week, making sure you prompt them often as to the day of the week and the segment of the day being discussed).

"Are there any activities you did during the last week that might be moderate, hard, or very hard that we've not already talked about?"

"Was this a typical week in terms of your usual pattern of activity or exercise?"

(If "No") "Were you more or less active in the past week than you usually are?"

(Page 3)

"Up to now, we've just been talking about the last 7 days. Now, I'd like you to think about your usual activities and your activities over the last three months. Here is a questionnaire for you to fill out that asks about what types of activities you have done. Let me know if you have any questions." (Give participant the Activities Questionnaire to fill out).

Appendix 2: General interviewing techniques

Presented below are general interviewing techniques. Specific issues regarding the 7-day PAR interview and solutions to a variety of problems are offered in Appendix 3.

I. HOW TO GET SATISFACTORY ANSWERS

A. ***Learn the Purpose of Each Question.*** In order to do a good job of interviewing; you need to understand the kind of information we are trying to get through particular question. Unless you understand its purpose, you will not be able to judge when response is adequate and when you must probe for clarification or for additional information.

B. ***Don't Attempt to Interpret/Explain the Question – Maintain Neutrality.*** If a participant does not seem to understand a question, repeat the question slowly and clearly. Give the participant time to think about the question (while simultaneously being aware of time allowed for administering the questionnaire). If a participant wants to know what a particular question means, and you do not have specific instructions for that question, the acceptable is: "Whatever it means to you." Do not attempt to explain the purpose of a question unless the interviewer instructions specifically authorize you to do so.

C. ***Don't leave a question until you have an adequate answer or have determined that a participant can't give a clearer answer.***

II. PROBING TECHNIQUES

The two most effective neutral probes are silence and repeating the original question.

A. ***Silence.*** The value of silence cannot be overestimated. Many people, including interviewers, react to silence as a vacuum that must be filled with constant chatter. The interviewer who can wait quietly and patiently will soon find that 15 seconds of silence is more that most participants can take, and the participant will often expand or clarify a previously inadequate answer.

B. ***Repeat the Question or Answer Categories.*** Be sure to repeat the question as stated in the interview script. This is particularly useful when the participant answers a question irrelevantly. In some cases it will be necessary to remind the participant of your frame of reference, i.e., to acknowledge what the participant has said and then bring the participant back to the topic by repeating the question.

C. ***Do not accept a "Don't Know" Answer Without Probing at Least Once.*** If a response is a "don't know", probe by asking: "Well, what do you think?" or "I'd like to know your opinion" (if the question asks for an opinion rather than facts.) If the question deals with facts, we prefer an approximation to no answer at all, and you might probe "what's your best guess?" or "approximately?" to convey the idea that 100% accuracy is not required.

D. ***Use Neutral Probes That Do Not Suggest Answers.*** Probes are needed to obtain more complete, accurate answers. All probes must be non-directive, i.e., the probe must not suggest any particular answer to the participant. Probes should be used whenever the participant is hesitant in answering questions; when he/she seems to

have trouble expressing himself/herself; when he/she seems too shy to speak at length; whenever there is any reason for the interviewer to believe that the participant has not given a complete report of his/her thoughts; and finally, reassuring probes are needed when a participant seems to lack confidence.

E. ***Examples of Other Neutral Probes:***
   1. In what way?
   2. What is that? Why do you feel that way?
   3. How do you mean?
   4. I would like your impression.
   5. I would like your opinion.
   6. What do you think?
   7. Can you give me an example? or For Example?
   8. Can you explain that in a little more detail?
   9. How are you using the term …..?
   10. How is that? Or How does that work?
   11. Anything at all – even little things?
   12. If you had to choose, which would you say?
   13. What else can you tell me about that?
   14. In general, overall …..

       1. Generally Speaking, Some Probes are Avoided in Favor of others
          a. Instead of "anything else?" you'll find that "what else can you tell me about that?" is more likely to elicit answers.
          b. Instead of "why?" you'll find "why do you feel that way?" or "I'd be interested in your reasons" accomplishes the same purpose and is less likely to be threatening.
       2. Questions Used in Ordinary Conversation Should be Avoided Because They Suggest Answers
          a. Refrain from asking "do you mean A or B". This suggests two possible answers and there may be others which may occur to the participant.

F. ***Do Not Leave a Probe Dangling.*** Always record the response to a probe even if it's Only "no" or "That's all I can think of."

G. ***Always Cross Reference.*** When you probe to clarify a response, always indicate which response you are clarifying. There will be times when a participant will say something ambiguous and continue talking.
   1. If there's not enough space to record the respondent's answer, use the margin. Be sure to label these continuations clearly when you edit each completed interview.
   2. Don't ask "do you mean…." People tend to say "yes" to any suggestion either because it's easy or because they think it's the right answer.

Appendix 3: PAR interview tips

- Participant says this wasn't a typical week, doesn't want to do recall on past week, or say information won't be valid. Tell participant there will be a question at the end of the questionnaire where we can note that it wasn't a typical week.
- If the participant isn't putting effort into the recall, take a different approach. Think back on (next day of the week) what did you get up and do on (next day of the week)? When the participant starts to put more effort into the recall, switch back to asking about anything moderate**,** hard or very hard during each segment of the day.
- Always get the participant to compare their activity to brisk walking, running, or in between walking and running.
- If the participant asks how an activity is classified, get as much information about the activity as possible and then tell them how it is usually classified.
- Assure the participant that it is all right to change answers or add forgotten items to the recall.
- Some participants will be ashamed or embarrassed of low activity levels. Assure them that different people have different activity levels.
- Some participants will apologize profusely if the interviewer has to erase or change an answer that has been given. Tell them that's why we do the interview in pencil and it's more important to get it right.
- Use cues that the participant may have provided during the interview to prompt their memories. If the participant just can't remember, go to the next time segment and at the end of the recall ask again about the missing time segment.
- Using Probing Tips to get complete information on an activity, its intensity, and duration.

Probing Tips

- Get as much detail as possible about an activity, its duration and its intensity, without exhausting the participant or getting bogged down.
- When a participant reports an activity, ask if they consider it moderate, hard, or very hard.
- Remember to liken moderate activity to going on a brisk walk. Hard activity is more than a brisk walk but not quire running. Very hard activity is the same intensity as running.
- Use the laminated cards to help classify activities.
- Ask "How long did you spend in that activity?" "Did you take any breaks?" Were you working at the same intensity level for the whole time?" Try and determine as closely as possible the actual time spent in an activity.
- If you're unsure of what comprises an activity (i.e., yard work), ask the participant to tell you the details of the activity. Determine which activities are moderate, hard, or very hard and record individual times in correct intensity categories.

- If you are unsure about how to classify an activity, refer to the Compendium of Physical Activities. If you need further help, call Debbie Young at JHU.
- The participant might report that this was a typical week for their pattern of activity. If the recall reflects some unusual activity (i.e., moving an office, cleaning the garage), ask the participant if they normally do (unusual activity) or something equal to that activity every week. If they answer 'no', then the past week was not a typical week. If they say 'yes' then the past seven days were typical.
- Look for facial clues for signs of boredom, confusion, and misunderstanding and adjust the interview accordingly.
- Listen attentively; things the interviewer hears at the first of the recall can be used to aid in the activity recall.
- Control the interview. It needs to be long enough to get the correct information, but not so long that time is wasted in meaningless conversation or useless details.
- Don't try to hide the recall form from the participant, but adopt a casual manner where the participant does not see the completed worksheet.
- Use the calendar to help the participant keep the days straight. If they have brought their own calendar they can use it to help them. Don't openly encourage participants to bring their calendars prior to a 7-day recall.

Appendix 4: Instructor's Outline

Introduction to Seven-Day PAR Training

Purpose

- To get an estimate of an individual's energy expenditure (including strength & flexibility activities) for previous week.
- Not singling out aerobic activities, looking at activities performed at various levels of energy expenditure.
- Most people spend majority of time doing light activity
- Exception: Stocking shelves at work (moderate)
- History of PAR

Interviewer Preparation Guidelines

Explain following items before beginning interview:

- Recall of actual activities for past week, not a history
- Not interested in light activities
- Have to be same or higher intensity as walking briskly

Categorization of activity

- Moderate – similar to how you feel when you're walking briskly
- Very Hard – similar to how you feel when you're running
- Hard – falls in between

Interview Protocol and Guidelines

Establishing days for recall

- Start with yesterday and work backwards (see manual)
- Label worksheet with days of the week

Sleep

- Start with yesterday and work backwards (see manual)
- Want an estimate of individual's hours in bed, not necessarily asleep
- Write total hours at top in that day's column – easier to wait until later to add up totals
- Prompt: ask if they have a regular time that they go to bed and get up, especially if they are having trouble remembering – also ask what they did that night to help them remember

Activity

- Start with yesterday and work backwards (see manual)

Appendix 5: List of activities and intensity levels

Compendium of Physical Activities: classification of energy costs of human physical activities

BARBARA E. AINSWORTH, WILLIAM L. HASKELL, ARTHUR S. LEON, DAVID R. JACOBS, JR., HENRY J. MONTOYE, JAMES F. SALLIS, and RALPH S. PAFFENBARGER, JR.

Division of Epidemiology,
School of Public Health (B.E.A., D.R.J., A.S.L.) and
Division of Kinesiology,
School of Kinesiology and Leisure Sciences (B.E.A., A.S.L.),
University of Minnesota,
Minneapolis, MN 55455;
Stanford Center for Research in Disease Prevention,
Stanford, CA 94305 (W.L.H.),-
Biodynamics Laboratory,
Department of Physical Education,
University of Wisconsin-Madison,
Madison WI 53706 (H.J.M.),-
Child and Family Development Health Studies,
Department of Pediatrics,
University of California-San Diego,
La Jolla, CA 92093 (J.F.S.),- and
School of Medicine,
Stan rd University,
Stanford, CA 94305 (R.S.P.)

ABSTRACT

AINSWORTH, B. E., W. L. HASKELL, A. S. LEON, D. R. JACOBS, JR., H. J. MONTOYE, J. F. SALLIS, and R. S. PAFFENBARGER, JR. Compendium of Physical Activities: classification of energy costs of human physical activities. Med. Sci. Sports Exerc., Vol. 25, No. 1, pp. 71-80, 1993. A coding scheme is presented for classifying physical activity by rate of energy expenditure, i.e., by intensity. Energy cost was established by a review of published and unpublished data. This coding scheme employs five digits that classify activity by purpose (i-e., sports, occupation, self-care), the specific type of activity, and its intensity as the ratio of work metabolic rate to resting metabolic rate (METs). Energy expenditure in kilocalories or kilocalories per kilogram body weight can be estimated for all activities, specific activities, or activity types. General use of this coding system would enhance the comparability of results across studies using self reports of physical activity.

EXERCISE, EXERTION, PHYSICAL ACTIVITY

The proliferation of self-report measures of physical activity reflects growing interest in the study of physical activity and its relation to various health outcomes. A common problem faced by researchers is the coding of physical activities by type and by intensity. Each researcher has devised a coding system to fit his or her purposes. While there are similarities across published systems, there are also differences that limit the comparability of results across studies and add confusion to the field. The availability of a comprehensive list of physical activities coded with a standardized system that is flexible enough to meet multiple needs of physical activity researchers would facilitate research in this area.

This Compendium of Physical Activities has been developed to facilitate the coding of physical activities and to promote comparability of coding across studies. The Compendium is designed to be useful for investigators who collect data on physical activity by diary, recall, or direct observation methods. The physical activity data may be used to describe activity patterns of populations, to study determinants of physical activity, or to investigate the relations between physical activity, health and disease. Because each activity can be coded by function, specific type, and intensity, the same compendium can be used for many different purposes and in both clinical and epidemiologic studies.

The intensity or energy cost values were derived from the best available published and unpublished data. Most sources have been used extensively by investigators in the past, but this Compendium has integrated these sources and offers a single coding system that can serve as a common source for subsequent research.

CODING SCHEME

This activity classification system was a product of a multicenter Request For Applications from the Epidemiology section of the National Heart, Lung, and Blood Institute (NHLBI) for the purpose of validating physical activity measurement techniques. It provides a comprehensive system for coding physical data on physical activity by purpose and energy cost. The energy cost of specific activities listed in this Compendium were obtained primarily from the following previously published physical activity energy expenditure lists: Tecumseh Occupational Questionnaire (13,14), Minnesota Leisure Time Physical Activity Questionnaire (LTPA) (5, 10), McArdle, Katch, and Katch's physical activity list (7,9), the 7-Day Recall Physical Activity Questionnaire (2), and the American Health Foundation's physical activity list (8). Activities from the LTPA were identified by a T followed by a number (e.g., T115). By retaining the LTPA designator codes, the new list may be used to score the LTPA with its original physical activity intensity codes.

As would be expected, there was considerable overlap in energy expenditure values among the supplied lists. For example, the Minnesota LTPA, which was developed from the Tecumseh Leisure Time Questionnaire, identifies similar activities; while the list of activities from the 7-Day Physical Activity Recall questionnaire is nearly identical to that of McArdle, Katch, and

Katch (9). In general, the majority of the energy expenditure lists were generated from Passmore and Durnin (11); while McArdle, Katch, and Katch (9) also used data derived from Bannister and Brown (1) and Howley and Glover (6).
The intensity assigned to activities in this publication were determined by selecting a mean energy expenditure value from the eight sources mentioned previously. The representative intensity levels were determined by consensus of the authors.

Organization

The Compendium of Physical Activities is organized to maximize flexibility in coding, data entry, and interpretation of energy cost for each class and type of activity.
Activity coding. The coding scheme for the Compendium of Activities employs a five-digit code in order to categorize activities by their major heading (first two digits on the left), specific activity (last three digits on the right), and intensity (3-digit column). The coding scheme is organized in the following way:

00	000	00.0
major headings	specific activity	intensity

For example

01	009	08.5
bicycling	bmx	METs

Major headings. The Compendium is organized by activity types or purpose and includes activities of daily living or self care, leisure and recreation, occupation, and rest (Table 1). The major headings explain the reason a person is engaging in a specific activity and is useful in categorizing activity types.

Identification of the proper major heading is the initial step in classifying an activity. However, it is possible that there may be more than one reason for performing an activity; thus, a specific activity may be listed under more than one major heading. For example, an individual may sit and read a book for pleasure in one situation and at another time read a document as a job requirement. These may be classified under the major headings of rest or inactivity and occupation depending on their purpose. Assumptions made for the placement of activities into major headings are listed in Appendix 2.

Specific activities. The specific activity descriptions range from a general classification of an activity (e.g., tennis, general) to a detailed description that includes the form and intensity of the activity (e.g., tennis, singles, vigorous effort) depending on the information gathered by the survey method. Activities without a specified intensity are classified as "general." More detailed descriptions of activities are preferred since an appropriate intensity can be assigned. Guidelines for coding specific activities within major headings are listed in Appendix 3.

Intensity of activities. All activities are assigned an intensity unit based on their rate of energy expenditure expressed as METS. The intensity of activities in the Compendium are classified as multiples of one MET or the ratio of the associated metabolic rate for the specific activity divided by the resting metabolic rate (RMR). For example, a 2-MET activity requires two times the metabolic energy expenditure of sitting quietly. One MET is also defined as the energy expenditure for sitting quietly, which for the average adult is approximately 3.5 ml of oxygen (kg body weight-1 (min-1 or 1 kcal (kg-1 body weight (h-1.

TABLE 1. Major types of activities

Bicycling	Lawn and garden	Sports
Conditioning exercises	Miscellaneous	Transportation
Dancing	Music playing	Walking
Fishing and hunting	Occupation	Water activities
Home activities	Running	Winter activities
Home repair	Self-Care	
Inactivity	Sexual activity	

A MET value was assigned to each activity in the Compendium and was based on the 'best representation" from published lists and selected unpublished data as was previously mentioned. For activities not in the original lists, intensity was obtained from published literature, if possible, and assigned a MET value or estimated from similar known activities (3,4,11,16).

Only data for adults were included in this Compendium, When children's games are listed in the Compendium, the intensity level is for adults participating in children's activities. Further, the Compendium is not intended to be used for adults with major neuromuscular handicaps or other conditions that would significantly alter their mechanical or metabolic efficiency.

Calculation of Energy Cost

Energy expenditure values can be expressed in kcal (kg-1 body weight (h-1, kcal (min-1, kcal (h-1, or kcal (24 h-1. The most accurate way to determine the kilocalorie energy cost of an activity is to measure the kcal expended during rest (i.e., the RMR) and multiply that value by the MET values listed in the Compendium. Because RMR is fairly close to 1 kcal (kg body weight-1 (h-1, the energy cost of activities may be expressed as multiples of the RMR (15). By multiplying the body weight in kg by the MET value and duration of activity, it is possible to estimate a kcal energy expenditure that it is specific to a person's body weight. For example, bicycling at a 4 MET value expends 4 kcal (kg-1 body weight (h-1. A 60-kg individual bicycling for 40 min expends the following: (4 METs x 60 kg body weight) x (40 min/60 min) = 160 kcal. Dividing 160 kcal by 40 min equals 4 kcal (min-1. Using the same formula for an 80-kg person would yield an energy expenditure of 213 kcal or 5.3 kcal (min-1. However, it is important to note that to the extent the RMR is not equal to 1 kcal (kg body weight-1 (h-1 for

individuals, then estimates of energy expenditure that include weight will more closely reflect body weight than the metabolic rate (2).

Use of the Compendium for PA Records or Diaries

For records or diaries the data collection forms should be organized in a way to identify each activity's major heading, classify the intensity level, and then record the duration to ensure accurate data entry. Figure 1 shows an example of a section of a data collection form that may be used for this purpose.
It is important the participant complete all questions except the space labeled "for clinic use only." The clinic staff will use this space to record the activity code or MET value for data analysis. The space labeled "reason for activity" is to help the coder decide under which major heading to place the activity. The intensity rating is designed to help the coder in assigning the appropriate MET value. Intensity terms of light, moderate, heavy or vigorous, and very heavy or very vigorous should be used in classifying intensity. In the case of walking, the corresponding intensity terms are very slow, slow, moderate, brisk, and very brisk. If a coder does not plan to use the five digit code for data analysis, a space can be provided on the questionnaire to record the MET values to calculate kcal scores.

Type of Activity	Reason for Activity	Subjective Intensity Level	Duration Hours:Min	Code or MET level (for clinic use only)
1. _____	_____	_____	_____	__ __ __ __ __
2. _____	_____	_____	_____	__ __ __ __ __
3. _____	_____	_____	_____	__ __ __ __ __

Figure 1 - Example of a section of recording form that asks participants to list the types of physical activities performed, reasons for engaging in the activities, a rating of the participants' impression of the intensity level (light, moderate, vigorous, very vigorous), and the duration of the activities in hours and minutes.

Discussion and Limitations

The Compendium of Activities is a classification system that groups physical activities by purpose and provides flexibility in determining energy cost. However, there are several factors that may limit the use of the Compendium for determining the precise energy cost of PA. The activity classification system was primarily based on previously published data and as such may not reflect the exact energy cost of all physical activities. Since often the values are merely averages, they do not take into account that some people perform activities more vigorously than others. In addition, the MET values of some activities were not derived from actual measurements of oxygen consumption; instead they were estimated from the energy cost of activities having similar movement patterns. Therefore, the estimates may have ill-defined confidence limits around the mean MET values. For activities in which the parameters are undefined, individual differences in energy expenditure can be large and the true energy cost for

a person may or may not be close to the stated mean. This does not reduce the value of the standard intensity codes, but it is an important perspective from which to view the Compendium. Calculation of kcal energy expenditure from body weight and MET values may also affect the energy cost of activities. Therefore, use of the kcal scores in correlation analyses should be used with caution since coefficients may reflect body weight rather than the actual energy cost of activities. Expression of energy expenditure scores as kcal (kg-1 body weight (h-1 or kcal (kg-1 body weight (day-1 will eliminate this effect. Individual variation in movement patterns and differences in the way activity is reported (i.e.. effort, pace, age, and gender differences) may influence the energy cost of activities also. For example, one person may rate his or her walking pace as "brisk" while another classifies the same pace as "slow." The Compendium cannot account for individual differences in movement efficiency; however, variation in how physical activities are recorded can be reduced by providing instruction to participants on how to classify energy expenditure (i.e., 3 mph is moderate walking), standardizing data recording techniques, and having trained interviewers review the data with participants for clarity before energy costs are calculated.

SUMMARY AND CONCLUSIONS

The Compendium of Physical Activities is a unique coding system that classifies the energy cost of physical activities. Based on previously published data, it groups activities by purpose and intensity expressed as METs. The Compendium is easy to use and provides flexibility in calculating the energy cost of various types of physical activities. Despite its possible limitations, the Compendium of Physical Activities is useful for coding physical activity questionnaires or records used in physical activity research, education, and clinic settings.

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Dr. Barbara Ainsworth was a post-doctoral associate in the Division of Epidemiology, School of Public Health, University of Minnesota at the time of this project. Dr. Ainsworth is currently with the Applied Physiology Laboratory, Department of Physical Education, Exercise and Sport Science, University of North Carolina at Chapel Hill.

Address for correspondence: Dr. Ainsworth, Department of Physical Education, Exercise, & Sport Science, CB #8700, Fetzer Gym, University of North Carolina at Chapel Hill, Chapel Hill, NG 27599-8700.

REFERENCES

1. BANNISTER, E. W. and S. R. BROWN. The relative energy requirements of physical activity. In: Exercise Physiology, H. B. Falls (Ed.), New York: Academic Press, 1968
2. BLAIR, S. N., W. L. HASKELL, P. Ho, et al. Assessment of habitual physical activity by a 7-day recall in a community survey and controlled experiment. Am. J. Epidemiol. 122:794-804, 1985
3. BURKE, E. J., J. A. AUCHINACHIE, R. HAYDEN, and J. M. LOFTIN. Energy cost of wheelchair basketball. Physician Sportsmed. 13:99-105
4. FISHER, S. V. and R. P- PATTERSON. Energy cost of ambulation with crutches. Arch. Phys. Med. Rehabil. 62:250-256, 1981
5. FOLSOM, A. R., C. J. CASPERSEN, H. L. TAYLOR, et al. Leisure time physical activity and its relationship to coronary risk factors in a population-based sample: the Minnesota Heart Survey. Am.J. EpidemioL. 121:570-579, 1985.
6. HOWLEY, E. T. and M. E. GLOVER. The caloric costs of running and walking one mile for men and women. Med. Sci. Sports Exerc. 6:235, 1974.
7. KATCH, F. I. and W. D. McARDLE. Nutrition, Weight Control, and Exercise, 3rd Ed. Philadelphia: Lea & Febiger, 1988.
8. LEON, A. S. Approximate energy expenditures and fitness values of sports and recreational and household activities, In: The Book of Health Physical Fitness. Chap. 5, E. L. Wynder (Ed.). 1981, pp.283-341,
9. McARDLE, W. D., F. I. KATCH, and V. L. KATCH. Exercise Physiology: Energy, Nutrition, and Human Performance, 2nd Ed. Philadelphia: Lea & Febiger, 1988, pp. 642-649,
10. MINNESOTA LEISURE TIME PHYSICAL ACTIVITY QUESTIONNAIRE MANUAL. Division of Epidemiology, School of Public Health, University of Minnesota. Minneapolis, MN 55455,
11. O'CONNELL, E. R., P. C. THOMAS, L. D. CADY, et al. Energy costs of simulated stair climbing as a job-related task in fire fighting. J Occup. Med. 28:282-284, 1986.
12. PASSMORE, R. and J. V. G. A. DURNIN. Human energy expenditure. Phvsiol Rev. 35:801-840, 1955.
13. REIFF, G. G., H. J. MONTOYE, R. D. REMINGTON, J. A. NAPIER, H. L. METZNER, and H. H. EPSTEIN. Assessment of physical activity by questionnaire and interview. In: Physical Activity and the Heart, M. J. Karvonen and A. J. Barry (Eds.). Springfield, IL: Charles C Thomas, 1967, pp. 336-371.
14. REIFF, G. G., H. J. MONTOYE, R. D. REMINGTON, J. A. NAPIER, H. L. METZNER, and F. H. EPSTEIN. Assessment of physical activity by questionnaire and interview. J. Sports Med. Phys. Fitness 7:1-32, 1967.
15 TAYLOR, H., D. R. JACOBS JR., B. SHUCKER, J. KNUDSEN, A. S. LEON, and G. DEBACKER. A questionnaire for the assessment of leisure time physical activities. J. Chronic Dis. 31:741,755, 1978.
16. TOWN, G. P., N. SOL, and W. E. SINNING. The effect of rope skipping rate on energy expenditure of males and females. Med. Sci. Sport Exerc. 12:295-298, 1980.

APPENDIX 1. Compendium of physical activities

Mets	Activity Level	Activity	Description
8.5	VH	Bicycling	Bicycling, BMX or mountain
4.0	M	Bicycling	Bicycling, <10 mph, general, leisure, to work or for pleasure
6.0	H	Bicycling	Bicycling, 10-11.9 mph, leisure, slow, light effort
8.0	VH	Bicycling	Bicycling, 12-13.9 mph, leisure, moderate effort
10.0	VH	Bicycling	Bicycling, 14-15.9 mph, racing or leisure, fast, vigorous effort
12.0	VH	Bicycling	Bicycling, 16-19 mph, racing/not drafting or > 19 mph drafting, very fast, racing general
16.0	VH	Bicycling	Bicycling, >20 mph, racing, not drafting
5.0	M	Bicycling	Unicycling
5.0	M	Conditioning exercise	Bicycling, stationary, general
3.0	M	Conditioning exercise	Bicycling, stationary, 50 W, very light effort
5.5	H	Conditioning exercise	Bicycling, stationary, 100 W, light effort
7.0	VH	Conditioning exercise	Bicycling, stationary, 150 W, moderate effort
10.5	VH	Conditioning exercise	Bicycling, stationary, 200 W, vigorous effort
12.5	VH	Conditioning exercise	Bicycling, stationary, 250 W, very vigorous effort
8.0	VH	Conditioning exercise	Calisthenics (e.g., pushups, pullups, situps), heavy, vigorous effort
4.5	M	Conditioning exercise	Calisthenics, home exercise, light or moderate effort, general (example: back exercises), going up and down from floor
8.0	VH	Conditioning exercise	Circuit training, general
6.0	H	Conditioning exercise	Weight lifting (free weight, nautilus or universal-type), power lifting or body building, vigorous effort
5.5	H	Conditioning exercise	Health club exercise, general (T 160)
6.0	H	Conditioning exercise	Stair-treadmill ergometer, general
9.5	VH	Conditioning exercise	Rowing, stationary ergometer, general
3.5	M	Conditioning exercise	Rowing, stationary, 50 W, light effort
7.0	VH	Conditioning exercise	Rowing, stationary, 100 W, moderate effort

8.5	VH	Conditioning exercise	Rowing, stationary, 150 W, vigorous effort
12.0	VH	Conditioning exercise	Rowing, stationary, 200 W, very vigorous effort
9.5	VH	Conditioning exercise	Ski machine, general
6.0	H	Conditioning exercise	Slimnastics
4.0	M	Conditioning exercise	Stretching, hatha yoga
6.0	H	Conditioning exercise	Teaching aerobic exercise class
4.0	M	Conditioning exercise	Water aerobics, water calisthenics
3.0	M	Conditioning exercise	Weight lifting (free, nautilus, or universal type), light or moderate effort, light workout, general
1.0		Conditioning exercise	Whirlpool, sitting
6.0	H	Dancing	Aerobic, ballet or modern, twist
6.0	H	Dancing	Aerobic, general
5.0	M	Dancing	Aerobic, low impact
7.0	VH	Dancing	Aerobic, high impact
4.5	M	Dancing	General
5.5	H	Dancing	Ballroom, fast (disco, folk, square)
3.0	M	Dancing	Ballroom, slow (e.g., waltz, foxtrot, slow dancing)
4.0	M	Fishing and hunting	Fishing, general
4.0	M	Fishing and hunting	Digging worms, with shovel
5.0	M	Fishing and hunting	Fishing from river bank and walking
2.5		Fishing and hunting	Fishing from boat, sitting
3.5	M	Fishing and hunting	Fishing from river bank, standing
6.0	H	Fishing and hunting	Fishing in stream, in waders
2.0		Fishing and hunting	Fishing, ice, sitting
2.5		Fishing and hunting	Hunting, bow and arrow or crossbow
6.0	H	Fishing and hunting	Hunting, deer, elk, large game
2.5		Fishing and hunting	Hunting, duck, wading
5.0	M	Fishing and hunting	Hunting, general
6.0	H	Fishing and hunting	Hunting, pheasants or grouse
5.0	M	Fishing and hunting	Hunting, rabbit, squirrel, prairie chick, raccoon, small game
2.5		Fishing and hunting	Pistol shooting or trap shooting, standing
2.5		Home activities	Carpet sweeping, sweeping floors
4.5	M	Home activities	Cleaning, heavy or major (e.g., wash car, wash windows, mop, clean garage), vigorous effort
3.5	M	Home activities	Cleaning, house or cabin, general

2.5		Home activities	Cleaning, light (dusting, straightening up, vacuuming, changing linen, carrying out trash), moderate effort
2.3		Home activities	Wash dishes-standing or in general (not broken into stand/walk components)
2.3		Home activities	Wash dishes; clearing dishes from the table-walking
2.5		Home activities	Cooking or food preparation-standing or sitting or in general (not broken into stand/walk components)
2.5		Home activities	Serving food, setting table-implied walking or standing
2.5		Home activities	Cooking or food preparation-walking
2.5		Home activities	Putting away groceries (e.g., carrying groceries, shopping without a grocery cart)
8.0	VH	Home activities	Carrying groceries upstairs
3.5	M	Home activities	Food shopping, with grocery cart
2.0		Home activities	Standing-shopping (non-grocery shopping)
2.3		Home activities	Walking-shopping (non-grocery shopping)
2.3		Home activities	Ironing
1.5		Home activities	Sitting, knitting, sewing, light wrapping (presents)
2.0		Home activities	Implied standing-laundry, fold or hang clothes, put clothes in washer or dryer, packing suitcase
2.3		Home activities	Implied walking-putting away clothes, gathering clothes to pack, putting away laundry
2.0		Home activities	Making bed
5.0	M	Home activities	Maple syruping/sugar bushing (including carrying buckets, carrying wood)
6.0	H	Home activities	Moving furniture, household
5.5	H	Home activities	Scrubbing floors, on hands and knees
4.0	M	Home activities	Sweeping garage, sidewalk or outside of house
7.0	VH	Home activities	Moving household items, carrying boxes
3.5	M	Home activities	Standing-packing/unpacking boxes, occasional lifting of household items, light-moderate effort
3.0	M	Home activities	Implied walking-putting away household items-moderate effort

9.0	VH	Home activities	Move household items upstairs, carrying boxes or furniture
2.5		Home activities	Standing-light (pump gas, change light bulb, etc.)
3.0	M	Home activities	Walking-light, non-cleaning (ready to leave, shut/lock doors, close windows, etc.)
2.5		Home activities	Sitting-playing with child(ren)-light
2.8		Home activities	Standing-playing with child(ren)-light
4.0	M	Home activities	Walk/run-playing with child(ren)-moderate
5.0	M	Home activities	Walk/run-playing with child(ren)-vigorous
3.0	M	Home activities	Child care: sitting/kneeling-dressing, bathing, grooming, feeding, occasional lifting of child-light effort
3.5	M	Home activities	Child care: standing-dressing, bathing, grooming, feeding, occasional lifting of child-light effort
3.0	M	Home repair	Airplane repair
4.5	M	Home repair	Automobile body work
3.0	M	Home repair	Automobile repair
3.0	M	Home repair	Carpentry, general, workshop
6.0	H	Home repair	Carpentry, outside house, installing rain gutters
4.5	M	Home repair	Carpentry, finishing or refinishing cabinets or furniture
7.5	VH	Home repair	Carpentry, sawing hardwood
5.0	M	Home repair	Caulking, chinking log cabin
4.5	M	Home repair	Caulking, except log cabin
5.0	M	Home repair	Cleaning gutters
5.0	M	Home repair	Excavating garage
5.0	M	Home repair	Hanging storm windows
4.5	M	Home repair	Laying or removing carpet
4.5	M	Home repair	Laying tile or linoleum
5.0	M	Home repair	Painting, outside house
4.5	M	Home repair	Painting, papering, plastering, scraping, inside house hanging sheet rock, remodeling
3.0	M	Home repair	Put on and removal of tarp-sailboat
6.0	H	Home repair	Roofing
4.5	M	Home repair	Sanding floors with a power sander
4.5	M	Home repair	Scrape and paint sailboat or powerboat
5.0	M	Home repair	Spreading dirt with a shovel

4.5	M	Home repair	Wash and wax hull of sailboat, car, powerboat, airplane
4.5	M	Home repair	Washing fence
3.0	M	Home repair	Wiring, plumbing
0.9		Inactivity, quiet	Lying quietly, reclining (watch television) lying quietly in bed-awake
1.0		Inactivity, quiet	Sitting quietly (riding in a car, listening to a lecture or music, watch television or a movie)
0.9		Inactivity, quiet	Sleeping
1.2		Inactivity, quiet	Standing quietly (standing in line)
1.0		Inactivity, light	Recline-writing
1.0		Inactivity, light	Recline-talking or talking on phone
1.0		Inactivity, light	Recline-reading
5.0	M	Lawn and garden	Carrying, loading or stacking wood, loading/unloading or carrying lumber
6.0	H	Lawn and garden	Chopping wood, splitting logs
5.0	M	Lawn and garden	Clearing land, hauling branches
5.0	M	Lawn and garden	Digging sandbox
5.0	M	Lawn and garden	Digging, spading, filling garden
6.0	H	Lawn and garden	Gardening with heavy power tools, tilling a garden (see occupation, shoveling)
5.0	M	Lawn and garden	Laying crushed rock
5.0	M	Lawn and garden	Laying sod
5.5	H	Lawn and garden	Mowing lawn, general
2.5		Lawn and garden	Mowing, lawn, riding mower
6.0	H	Lawn and garden	Mowing lawn, walk, hand mower
4.5	M	Lawn and garden	Mowing lawn, walk, power mower
4.5	M	Lawn and garden	Operating snow blower, walking
4.0	M	Lawn and garden	Planting seedlings, shrubs
4.5	M	Lawn and garden	Planting trees
4.0	M	Lawn and garden	Raking lawn
4.0	M	Lawn and garden	Raking roof with snow rake
3.0	M	Lawn and garden	Riding snow blower
4.0	M	Lawn and garden	Sacking grass, leaves
6.0	H	Lawn and garden	Shoveling, snow, by hand
4.5	M	Lawn and garden	Trimming shrubs or trees, manual cutter
3.5	M	Lawn and garden	Trimming shrubs or trees, power cutter
2.5		Lawn and garden	Walking, applying fertilizer or seeding a lawn
1.5		Lawn and garden	Watering lawn or garden, standing or walking

4.5	M	Lawn and garden	Weeding cultivating garden
5.0	M	Lawn and garden	Gardening, general
3.0	M	Lawn and garden	Implied walking/standing-picking up yard, light
1.5		Miscellaneous	Sitting, card playing, playing board game
2.0		Miscellaneous	Standing-drawing (writing), casino gambling
1.3		Miscellaneous	Sitting-reading book, newspaper, etc.
1.8		Miscellaneous	Sitting-writing, desk work
1.8		Miscellaneous	Standing-talking or talking on the phone
1.5		Miscellaneous	Sitting-talking or talking on the phone
1.8		Miscellaneous	Sitting-studying, general, including reading and /or writing
1.8		Miscellaneous	Sitting-in class, general, including note-taking or class discussion
1.8		Miscellaneous	Standing-reading
1.8		Music playing	Accordion
2.0		Music playing	Cello
2.5		Music playing	Conducting
4.0	M	Music playing	Drums
2.0		Music playing	Flute (sitting)
2.0		Music playing	Horn
2.5		Music playing	Piano or organ
3.5	M	Music playing	Trombone
2.5		Music playing	Trumpet
2.5		Music playing	Violin
2.0		Music playing	Woodwind
2.0		Music playing	Guitar, classical, folk (sitting)
3.0	M	Music playing	Guitar, rock and roll band (standing)
4.0	M	Music playing	Marching band, playing an instrument, baton twirling (walking)
3.5	M	Music playing	Marching band, drum major (walking)
4.0	M	Occupation	Bakery, general
2.3		Occupation	Bookbinding
6.0	H	Occupation	Building road (including hauling debris, driving heavy machinery)
2.0		Occupation	Building road, directing traffic (standing)
3.5	M	Occupation	Carpentry, general
8.0	VH	Occupation	Carrying heavy loads, such as bricks
8.0	VH	Occupation	Carrying moderate loads up stairs, moving boxes (16-40 pounds)
2.5		Occupation	Chambermaid

6.5	H	Occupation	Coal mining, drilling coal, rock
6.5	H	Occupation	Coal mining, erecting supports
6.0	H	Occupation	Coal mining, general
7.0	VH	Occupation	Coal mining, shoveling coal
5.5	H	Occupation	Construction, outside, remodeling
3.5	M	Occupation	Electric work, plumbing
8.0	VH	Occupation	Farming, baling hay, cleaning barn, poultry work
3.5	M	Occupation	Farming, chasing cattle, non-strenuous
2.5		Occupation	Farming, driving harvester
2.5		Occupation	Farming, driving tractor
4.0	M	Occupation	Farming, feeding small animals
4.5	M	Occupation	Farming, feeding cattle
8.0	VH	Occupation	Farming, forking straw bales
3.0	M	Occupation	Farming, milking by hand
1.5		Occupation	Farming, milking by machine
5.5	H	Occupation	Farming, shoveling grain
12.0	VH	Occupation	Fire fighter, general
11.0	VH	Occupation	Fire fighter, climbing ladder with full gear
8.0	VH	Occupation	Fire fighter, hauling hoses on ground
17.0	VH	Occupation	Forestry, ax chopping, fast
5.0	M	Occupation	Forestry, ax chopping, slow
7.0	VH	Occupation	Forestry, barking trees
11.0	VH	Occupation	Forestry, carrying logs
8.0	VH	Occupation	Forestry, felling trees
8.0	VH	Occupation	Forestry, general
5.0	M	Occupation	Forestry, hoeing
6.0	H	Occupation	Forestry, planting by hand
7.0	VH	Occupation	Forestry, sawing by hand
4.5	M	Occupation	Forestry, sawing, power
9.0	VH	Occupation	Forestry, trimming trees
4.0	M	Occupation	Forestry, weeding
4.5	M	Occupation	Furriery
6.0	H	Occupation	Horse grooming
8.0	VH	Occupation	Horse racing, galloping
6.5	H	Occupation	Horse racing, trotting
2.6		Occupation	Horse racing, walking
3.5	M	Occupation	Locksmith
2.5		Occupation	Machine tooling, machining, working sheet metal
3.0	M	Occupation	Machine tooling, operating lathe
5.0	M	Occupation	Machine tooling, operating punch press

4.0	M	Occupation	Machine tooling, tapping and drilling
3.0	M	Occupation	Machine tooling, welding
7.0	VH	Occupation	Masonry, concrete
4.0	M	Occupation	Masseur, masseuse (standing)
7.0	VH	Occupation	Moving, pushing heavy objects, 75 lbs or more (desks, moving van work)
2.5		Occupation	Operating heavy duty equipment/automated, not driving
4.5	M	Occupation	Orange grove work
2.3		Occupation	Printing (standing)
2.5		Occupation	Police, directing traffic (standing)
2.0		Occupation	Police, driving a squad car (sitting)
1.3		Occupation	Police, riding in a squad car (sitting)
8.0	VH	Occupation	Police, making an arrest (standing)
2.5		Occupation	Shoe repair, general
8.5	VH	Occupation	Shoveling, digging ditches
9.0	VH	Occupation	Shoveling, heavy (more than 16 lbs. $\cdot$ min^{-1})
6.0	H	Occupation	Shoveling, light (less than 10 lbs. $\cdot$ min^{-1})
7.0	VH	Occupation	Shoveling, moderate (10-15 lbs. $\cdot$ min^{-1})
1.5		Occupation	Sitting-light office work, in general (chemistry lab work, light use of handtools, watch repair or micro-assembly, light assembly/repair)
1.5		Occupation	Sitting-meetings, general, and/or with talking involved
2.5		Occupation	Sitting; moderate (heavy levers, riding mower/forklift, crane operation)
2.5		Occupation	Standing; light (bartending, store clerk, assembling, filing, xeroxing, put up Christmas tree)
3.0	M	Occupation	Standing; light/moderate (assemble/repair heavy parts, welding, stocking, auto repair, pack boxes for moving, etc.), patient care (as in nursing)
3.5	M	Occupation	Standing; moderate (assembling at fast rate, lifting 50 lbs, hitch/twisting ropes)
4.0	M	Occupation	Standing; moderate/heavy (lifting more than 50 lb, masonry, painting, paper hanging)
5.0	M	Occupation	Steel mill, fetting
5.5	H	Occupation	Steel mill, forging
8.0	VH	Occupation	Steel mill, hand rolling
8.0	VH	Occupation	Steel mill, merchant mill rolling

11.0	VH	Occupation	Steel mill, removing slag
7.5	VH	Occupation	Steel mill, tending furnace
5.5	H	Occupation	Steel mill, tipping molds
8.0	VH	Occupation	Steel mill, working in general
2.5		Occupation	Tailoring, cutting
2.5		Occupation	Tailoring, general
2.0		Occupation	Tailoring, hand sewing
2.5		Occupation	Tailoring, machine sewing
4.0	M	Occupation	Tailoring, pressing
6.5	H	Occupation	Truck driving, loading and unloading truck (standing)
1.5		Occupation	Typing, electric, manual or computer
6.0	H	Occupation	Using heavy power tools such as pneumatic tools (jackhammers, drills, etc.)
8.0	VH	Occupation	Using heavy tools (not power) such as shovel, pick, tunnel bar, spade
2.0		Occupation	Walking on job, less than 2.0 mph (in office or lab area), very slow
3.5	M	Occupation	Walking on job, 3.0 mph, in office, moderate speed, not carrying anything
4.0	M	Occupation	Walking on job, 3.5 mph, in office, brisk speed, not carrying anything
3.0	M	Occupation	Walking, 2.5 mph, slowly and carrying light objects less than 25 lbs
4.0	M	Occupation	Walking, 3.0 mph, moderately and carrying light objects less than 25 lbs
4.5	M	Occupation	Walking, 3.5 mph, briskly and carrying objects less than 25 lbs
5.0	M	Occupation	Walking or walk downstairs or standing, carrying objects about 25-49 lbs
6.5	H	Occupation	Walking or walk downstairs or standing, carrying objects about 50-74 lbs
7.5	VH	Occupation	Walking or walk downstairs or standing, carrying objects about 75-99 lbs
8.5	VH	Occupation	Walking or walk downstairs or standing, carrying objects about 100 lbs and over
3.0	M	Occupation	Working in scene shop, theater actor, backstage, employee
6.0	H	Running	Jog/walk combition (jogging component of less than 10 min) (T 180)
7.0	VH	Running	Jogging, general
8.0	VH	Running	Running, 5 mph (12 min·mile^{-1})

9.0	VH	Running	Running, 5.2 mph (11.5 min·mile^{-1})
10.0	VH	Running	Running, 6 mph (10 min·mile^{-1})
11.0	VH	Running	Running, 6.7 mph (9 min·mile^{-1})
11.5	VH	Running	Running, 7 mph (8.5 min·mile^{-1})
12.5	VH	Running	Running, 7.5 mph (8 min·mile^{-1})
13.5	VH	Running	Running, 8 mph (7.5 min·mile^{-1})
14.0	VH	Running	Running, 8.6 mph (7 min·mile^{-1})
15.0	VH	Running	Running, 9 mph (6.5 min·mile^{-1})
16.0	VH	Running	Running, 10 mph (6 min·mile^{-1})
18.0	VH	Running	Running, 10.9 mph (5.5 min·mile^{-1})
9.0	VH	Running	Running, cross-country
8.0	VH	Running	Running, general
8.0	VH	Running	Running, in place
15.0	VH	Running	Running, stairs, up
10.0	VH	Running	Running, on a track, team practice
8.0	VH	Running	Running, training, pushing wheelchair, marathon wheeling
3.0	M	Running	Running, wheeling, general
2.5		Self-care	Standing-getting ready for bed, in general
1.0		Self-care	Sitting on toilet
2.0		Self-care	Bathing (sitting)
2.5		Self-care	Dressing, undressing (standing or sitting)
1.5		Self-care	Eating (sitting)
2.0		Self-care	Talking and eating or eating only (standing)
2.5		Self-care	Sitting or standing – grooming (washing, shaving, brushing teeth, urinating, washing hands, put on make-up)
4.0	M	Self-care	Showering, toweling off (standing)
1.5		Sexual activity	Active, vigorous effort
1.3		Sexual activity	General, moderate effort
1.0		Sexual activity	Passive, light effort, kissing, hugging
3.5	M	Sports	Archery (non-hunting)
7.0	VH	Sports	Badminton, competitive
4.5	M	Sports	Badminton, social singles and doubles, general
8.0	VH	Sports	Basketball, game
6.0	H	Sports	Basketball, nongame, general
7.0	VH	Sports	Basketball, officiating
4.5	M	Sports	Basketball, shooting baskets
6.5	H	Sports	Basketball, wheelchair
2.5		Sports	Billiards
3.0	M	Sports	Bowling

12.0	VH	Sports	Boxing, in ring, general
6.0	H	Sports	Boxing, punching bag
9.0	VH	Sports	Boxing, sparring
7.0	VH	Sports	Broomball
5.0	M	Sports	Children's games (hopscotch, 4-square, dodgeball, playground apparatus, t-ball, tetherball, marbles, jacks, arcade games
4.0	M	Sports	Coaching: football, soccer, basketball, baseball, swimming, etc.
5.0	M	Sports	Cricket (batting, bowling)
2.5		Sports	Croquet
4.0	M	Sports	Curling
2.5		Sports	Darts, wall or lawn
6.0	H	Sports	Drag racing, pushing or driving a car
6.0	H	Sports	Fencing
9.0	VH	Sports	Football, competitive
8.0	VH	Sports	Football, touch, flag, general
2.5		Sports	Football or baseball, playing catch
3.0	M	Sports	Frisbee playing, general
3.5	M	Sports	Frisbee, ultimate
4.5	M	Sports	Golf, general
5.5	H	Sports	Golf, carrying clubs
3.0	M	Sports	Golf, miniature, driving range
5.0	M	Sports	Golf, pulling clubs
3.5	M	Sports	Golf, using power cart
4.0	M	Sports	Gymnastics, general
4.0	M	Sports	Hacky sack
12.0	VH	Sports	Handball, general
8.0	VH	Sports	Handball, team
3.5	M	Sports	Hang gliding
8.0	VH	Sports	Hockey, field
8.0	VH	Sports	Hockey, ice
4.0	M	Sports	Horseback riding, general
3.5	M	Sports	Horseback riding, saddling horse
6.5	H	Sports	Horseback riding, trotting
2.5		Sports	Horseback riding, walking
3.0	M	Sports	Horseshoe pitching, quoits
12.0	VH	Sports	Jai alai
10.0	VH	Sports	Judo, jujitsu, karate, kick boxing, tae kwan do
4.0	M	Sports	Juggling
7.0	VH	Sports	Kickball

8.0	VH	Sports	Lacrosse
4.0	M	Sports	Motocross
9.0	VH	Sports	Orienteering
10.0	VH	Sports	Paddleball, competitive
6.0	H	Sports	Paddleball, casual, general
8.0	VH	Sports	Polo
10.0	VH	Sports	Racketball, competitive
7.0	VH	Sports	Racketball, casual, general
11.0	VH	Sports	Rock climbing, ascending rock
8.0	VH	Sports	Rock climbing, rappelling
12.0	VH	Sports	Rope jumping, fast
10.0	VH	Sports	Rope jumping, moderate, general
8.0	VH	Sports	Rope jumping, slow
10.0	VH	Sports	Rugby
3.0	M	Sports	Shuffleboard, lawn bowling
5.0	M	Sports	Skateboarding
7.0	VH	Sports	Skating, roller
3.5	M	Sports	Sky diving
10.0	VH	Sports	Soccer, competitive
7.0	VH	Sports	Soccer, casual, general
5.0	M	Sports	Softball or baseball, fast or slow pitch, general
4.0	M	Sports	Softball, officiating
6.0	H	Sports	Softball, pitching
12.0	VH	Sports	Squash
4.0	M	Sports	Table tennis, ping pong
4.0	M	Sports	Tai chi
7.0	VH	Sports	Tennis, general
6.0	H	Sports	Tennis, doubles
8.0	VH	Sports	Tennis, singles
3.5	M	Sports	Trampoline
4.0	M	Sports	Volleyball, competitive, in gymnasium
3.0	M	Sports	Volleyball, noncompetitive; 6-9 member team, general
8.0	VH	Sports	Volleyball, beach
6.0	H	Sports	Wrestling (one match = 5 min)
7.0	VH	Sports	Wallyball, general
2.0		Transportation	Automobile or light truck (not a semi) driving
2.0		Transportation	Flying airplane
2.5		Transportation	Motor scooter, motorcycle

6.0	H	Transportation	Pushing plane in and out of hangar
3.0	M	Transportation	Driving heavy truck, tractor, bus
7.0	VH	Walking	Backpacking, general
3.5	M	Walking	Carrying infant or 15-lb load (e.g., suitcase), level ground or downstairs
9.0	VH	Walking	Carrying load upstairs, general
5.0	M	Walking	Carrying 1- to 15-lb load, upstairs
6.0	H	Walking	Carrying 16- to 24-lb load, upstairs
8.0	VH	Walking	Carrying 25- to 49-lb load, upstairs
10.0	VH	Walking	Carrying 50- to 74-lb load, upstairs
12.0	VH	Walking	Carrying 74+ lb load, upstairs
7.0	VH	Walking	Climbing hills with 0- to 9-lb load
7.5	VH	Walking	Climbing hills with 10- to 20-lb load
8.0	VH	Walking	Climbing hills with 21- to 42-lb load
9.0	VH	Walking	Climbing hills with 42+ lb load
3.0	M	Walking	Downstairs
6.0	H	Walking	Hiking, cross country
6.5	H	Walking	Marching, rapidly, military
2.5		Walking	Pushing or pulling stroller with child
6.5	H	Walking	Race walking
8.0	VH	Walking	Rock or mountain climbing
8.0	VH	Walking	Up stairs, using or climbing up ladder
4.0	M	Walking	Using crutches
2.0		Walking	Walking, less than 2.0 mph, level ground, strolling, household walking, very slow
2.5		Walking	Walking, 2.0 mph, level, slow pace, firm surface
3.0	M	Walking	Walking, 2.5 mph, firm surface
3.0	M	Walking	Walking, 2.5 mph, downhill
3.5	M	Walking	Walking, 3.0 mph, level, moderate pace, firm surface
4.0	M	Walking	Walking, 3.5 mph, level, brisk, firm surface
6.0	H	Walking	Walking, 3.5 mph, uphill
4.0	M	Walking	Walking, 4.0 mph, level, firm surface, very brisk pace
4.5	M	Walking	Walking, 4.5 mph, level, firm surface, very, very brisk
3.5	M	Walking	Walking, for pleasure, work break, walking the dog
5.0	M	Walking	Walking, grass track
4.0	M	Walking	Walking, to work or class

2.5		Water activities	Boating, power
4.0	M	Water activities	Canoeing, on camping trip
7.0	VH	Water activities	Canoeing, portaging
3.0	M	Water activities	Canoeing, rowing, 2.0-3.9 mph, light effort
7.0	VH	Water activities	Canoeing, rowing, 4.0-5.9 mph, moderate effort
12.0	VH	Water activities	Canoeing, rowing, >6 mph, vigorous effort
3.5	M	Water activities	Canoeing, rowing, for pleasure, general
12.0	VH	Water activities	Canoeing, rowing, in competition, or crew or sculling
3.0	M	Water activities	Diving, springboard or platform
5.0	M	Water activities	Kayaking
4.0	M	Water activities	Paddleboat
3.0	M	Water activities	Sailing, boat and board sailing, windsurfing, ice sailing, general
5.0	M	Water activities	Sailing, in competition
3.0	M	Water activities	Sailing, Sunfish/Laser/Hobie Cat, keel boats, ocean sailing, yachting
6.0	H	Water activities	Skiing, water
7.0	VH	Water activities	Skimobiling
12.0	VH	Water activities	Skindiving or scuba diving as frogman
16.0	VH	Water activities	Skindiving, fast
12.5	VH	Water activities	Skindiving, moderate
7.0	VH	Water activities	Skindiving, scuba diving, general (T 310)
5.0	M	Water activities	Snorkeling
3.0	M	Water activities	Surfing, body or board
10.0	VH	Water activities	Swimming laps, freestyle, fast, vigorous effort
8.0	VH	Water activities	Swimming laps, freestyle, slow, moderate or light effort
8.0	VH	Water activities	Swimming, backstroke, general
10.0	VH	Water activities	Swimming, breaststroke, general
11.0	VH	Water activities	Swimming, butterfly, general
11.0	VH	Water activities	Swimming, crawl, fast (75 yards·min^{-1}), vigorous effort
8.0	VH	Water activities	Swimming, crawl, slow (50 yards·min^{-1}), moderate or light effort
6.0	H	Water activities	Swimming, lake, ocean, river (T 280, T 295)
6.0	H	Water activities	Swimming, leisurely, not lap swimming, general
8.0	VH	Water activities	Swimming, sidestroke, general

8.0	VH	Water activities	Swimming, synchronized
10.0	VH	Water activities	Swimming, treading water, fast, vigorous effort
4.0	M	Water activities	Swimming, treading water, moderate effort, general
10.0	VH	Water activities	Water polo
3.0	M	Water activities	Water volleyball
5.0	M	Water activities	Whitewater rafting, kayaking, or canoeing
6.0	H	Winter activities	Moving ice house (set up/drill holes, etc.)
5.5	H	Winter activities	Skating, ice, 9 mph or less
7.0	VH	Winter activities	Skating, ice, general
9.0	VH	Winter activities	Skating, ice, rapidly, more than 9 mph
15.0	VH	Winter activities	Skating, speed, competitive
7.0	VH	Winter activities	Ski jumping (climb up carrying skis)
7.0	VH	Winter activities	Skiing, general
7.0	VH	Winter activities	Skiing, cross-country, 2.5 mph, slow or light effort, ski walking
8.0	VH	Winter activities	Skiing, cross-country, 4.0-4.9 mph, moderate speed and effort, general
9.0	VH	Winter activities	Skiing, cross-country, 5.0-7.9 mph, brisk speed, vigorous effort
14.0	VH	Winter activities	Skiing, cross-country, >8.0 mph, racing
16.5	VH	Winter activities	Skiing, cross-country, hard snow, uphill, maximum
5.0	M	Winter activities	Skiing, downhill, light effort
6.0	H	Winter activities	Skiing, downhill, moderate effort, general
8.0	VH	Winter activities	Skiing, downhill, vigorous effort, racing
7.0	VH	Winter activities	Sledding, tobogganing, bobsledding, luge
8.0	VH	Winter activities	Snow shoeing
3.5	M	Winter activities	Snowmobiling

APPENDIX 2. Guidelines for assigning activities by major purpose or intent

1. Conditioning exercises include activities with the intent of improving physical condition. This includes stationary ergometers (bicycling, rowing machines, treadmills, etc.) health club exercise, calisthenics, and aerobics.
2. Home repair includes all activity associated with the repair of a house and does not include housework. This is not an occupational task.
3. Sleeping, lying, sitting, and standing are classified as inactivity.
4. Home activities include all activities associated with maintaining the inside of a home and includes house cleaning, laundry, grocery shopping, and cooking.
5. Lawn and garden includes all activity associated with maintaining the yard and includes

yard work, gardening, and snow removal.

6. Occupation includes all job-related physical activity where one is paid (gainful employment). Specific activities may be cross-referenced in other categories (such as reading, writing, driving a car, waking) and should be coded in this major heading if related to employment. Housework is occupational only if the person is earning money for the task.
7. Self-care includes all activity related to grooming, eating, bathing, etc.
8. Transportation includes energy expended for the primary purpose of going somewhere in a motorized vehicle.

APPENDIX 3. Guidelines for coding specific activities.

A. General guidelines: All activities should be coded as "general" if no other information about the activity is given. This applies primarily to intensity ranges. If any additional information is given, activities should be coded accordingly.

B. Specific guidelines

1. Bicycling
    a. Stationary cycling using cycle ergometers (all types), wind trainers, or other conditioning devices should be classified under the major heading of Conditioning Exercise, stationary cycling specific activities (codes 02010 to 02015).
    b. The list does not account for differences in wind conditions.
    c. If bicycling is performed in a race, classify it as general racing if no descriptions are given about drafting (code 01050). If information is given about the speed or drafting code as 01050 (bicycling, 16-19 mph, racing/not drafting or >19 mph drafting, very fast) or 01060 (bicycling, ≥a2O mph, racing, not drafting).
    d Using a mountain bike in the city should be classified as bicycling, general (code 01010). Cycling on mountain trails or on a BMX course is coded 01009.
2. Conditioning Exercises
    a. If a calisthenics program is described as a light or moderate type of activity (e.g., performing back exercises) but indicates a vigorous effort on the part of the participant, code the activity as calisthenics, general (code 02030).
    b. Exercise performed at a health club that is not described should be classified as health club, general (code 02060). Other activities performed at a health club (e.g., weight lifting, aerobic dance, circuit training, treadmill running, etc. at a health club) should be classified under separate major headings.
    c. Regardless of whether aerobic dance, conditioning, circuit training, or water calisthenics programs are described by their component parts (i.e., 10 min jogging in place, 10 min sit-ups, 10 min stretching, etc.), code the

activity as one activity (e.g., water aerobics, code 02120).

d. Effort, speed, or intensity breakdowns for the specific activities of stair-treadmill ergometer (code 02065), ski machine (code 02080), water aerobics or water calisthenics (code 02120), circuit training (code 02040), and slimnastics (code 02090) are not given. Code these as general, even though effort or intensities may vary in the descriptions of the activity.

3. Dancing
   a. If the type of dancing preformed is not described, code it as dancing, general (code 03025)-
4. Home Activities
   a. House cleaning should be coded as light (code 05040) or heavy (code 05020). Examples for each are given in the description of the specific activities.
   b. Making the bed on a daily basis is coded 05100. Changing the bed sheets is coded as cleaning, light (code 05040).
5. Home Repair
   a. Any painting outside of the house (i.e., fence, the house, barn) is coded, painting, outside house (code 60150).
6. Inactivity
   a. Sitting and reading a book or newspaper is listed under the major heading of Miscellaneous, reading, book, newspaper, etc. (code 09030).
   b. Sitting and writing is listed under the major heading of Miscellaneous, writing (code 09040).
7. Lawn and Garden
   a. Working in the garden with a specific type of tool (e.g., hoe, spade) is coded as digging, spading, filling garden (code 08050).
   b. Removing snow may be done by one of three methods: shoveling snow by hand (code 08200), walking and operating a snow blow (code 08130), or riding a snow blower (code 08180).
8. Music Playing
   a. Most variation in music playing will be according to the setting (i.e., rock and roll band, orchestra, marching band, concert band, standing on the stage, performance, practice, in a church etc.). The compendium does not consider differences in the setting (except for marching band and guitar playing).
9. Occupation
   a. Types of occupational activities not listed separately under specific activities (e.g., chemistry laboratory experiments), should be placed into the types of energy expenditure classifications best describing the activity. See sitting: light (code 11580), sitting: moderate (code 11590), standing: light (code 11600), standing: light to moderate (code 11610) standing: moderate (code 11620), standing: moderate to heavy code 11630).
   b. Driving an automobile or a light truck for employment (taxi cab, salesman, contractor, ambulance driver, bus driver, should be listed under

the major heading of Transportation, automobile or light truck (not a semi) driving (code 06010).

c. Performing skin or SCUBA diving as an occupation is listed under the major heading of Water Activities, and the specific activity of skin-diving or SCUBA diving as a frogman (code 18170).

10. Running
    a. Running is not classified as treadmill or outdoor running. Running on a treadmill or outdoors should be coded by the speed of the run (codes 12030 to 12130). If speed is not given, code it as running, general (code 12150).
11. Self-care
    a. The compendium does not account for effort ratings. All items are considered to be general.
12. Transportation
    a. Being a passenger in an automobile s coded under the major heading of inactivity, sitting quietly (code 07020).
13. Walking
    a. Household walking is coded 17150, regardless if the subject identified a walking speed.
    b. If the walking speed is unidentified, use 3.0 mph, level, moderate, firm surface as the standard speed (code 17190). This should not be used for household waking.
    c. Walking during a household move, shopping, or for household work is coded under the major heading of Home Activities. Waking for job related activities is coded under Occupational Activities.
    d. If a subject is backpacking, regardless of descriptors attached, the code is backpacking, general (code 17010).
    e. The compendium does not account for variaitons in speed or effort while carrying luggage or a child.
    f. Mountain climbing should be classified as general (rock or mountain climbing, code 17120) if no descriptors are given. If the weight of the load is described, code the activity as climbing hills with the appropriate load (codes 17030 to 17060).
    g. Waking on a grassy area (golf course, in a park, etc.) should be coded as walking, grass track (code 17260). The compendium does not account for variations in waking speed on a grassy area, so ignore recordings of walking speed or effort. If the walking is not on a grassy area, code the activity according to the walking speed (codes 17150 to 17230).
    h. Waking to work or to class should be coded as 17270. The compendium does not account for walking speed or effort in this activity. Even though a speed or effort is given for the walking, do not code walking to work or to class in any other walking category.
    i. Hiking and cross-country waking (code 17080) should be used only if the walking activity lasted 3 h or more. Do not use this category for

backpacking, but for day hikes.

14. Water Activities
    a. Swimming should be coded as leisurely, not lap swimming (code 18310) if descriptions about stroke, speed, or swimming location are not given-
    b. Lap swimming should be coded as swimming laps, freestyle, slow (code 18240) if the activity is described as lap swimming, light or moderate effort, but stroke or speed are not indicated. Swimming laps should be coded as swimming, laps, freestyle, fast (code 18230) if the activity is described as lap swimming, vigorous effort but stoke or speed are not indicated given.
    c. Swimming crawl should be coded as swimming, crawl, slow (50 yards $\cdot$ min^{-1}) if speed is not given and the effort is rated light or moderate (code 18290). Swimming crawl should be coded as swimming, crawl, fast (75 yards $\cdot$ min^{-1}) if speed is not given, but the effort is rated as vigorous (code 18280).
    d. The swimming stokes of backstroke (code 18250), breaststroke (code 18260), butterfly (code 18270), and sidestroke (code 18230) are coded as general for speed and intensity.
    e. If a swimming activity is not identified as lake, ocean, or river swimming (code 18300), assume that the swimming was performed in a swimming pool.
    f. If canoeing is related to a canoe trip, code as canoeing, on a camping trip (code 18020). Otherwise, code it according to the speed and effort listed.

Summary of Edits

Summary of changes between Version 1.0 and Version 1.1:

- Corrected schedule for administration of Rose Angina Questionnaire (completed at 3 and 12 months in addition to baseline, 6, and 18 months.)
- Added instructions for allowing a participant to follow PREMIER exercise recommendations for a positive Rose Angina Questionnaire after baseline.
- Added heart rate contraindications for performing treadmill testing.
- Added instructions for cool down following early termination of treadmill testing.
- Added that staff are requested to make at least 3 attempts to reach the participant to determine the resolution of a referral to a personal physician for reaching escape BP.

Summary of changes between Version 1.1 and Version 1.2:

- Systematic review of participants' medical records to detect adverse events is not allowed; however, if a medical record is reviewed for documentation of an adverse event and evidence of an unreported adverse event is found, an AE Form (#30) should be completed and reported to the CC.

Summary of changes between Version 1.2 and Version 1.3:

- Modified section on symptom and AE surveillance to reflect new definitions of AEs.
- An AE form is completed at 18 months for physician confirmed angina
- Added information on NIH requirements for reporting DSMB review of adverse events to IRBs.
- For participants with out-of-range pre-exercise heart rates, the study clinician assesses if the treadmill is performed as scheduled, rescheduled till heart rate is within range, or the participant is referred to his or her personal physician for a safety assessment.

Summary of changes between Version 1.3 and Version 1.4:

- Added referral to physician for further evaluation within two months for BP $\geq$ 140/90 to escape level 1 at the 12-month visit.

23. Safety Monitoring

Blood Pressure

To prevent a prolonged period of untreated hypertension (outside the eligibility range of PREMIER), several blood pressure safety procedures are implemented.

- At PSV, individuals taking any anti-hypertensive medications are excluded, and those who report having taken them must have been off medication for at least three months.
- Individuals with a history of cerebrovascular or cardiovascular disease are excluded, as are those with congestive heart failure, diabetes, and renal insufficiency.
- Blood pressure is monitored regularly throughout the study, and "escape levels" are established to identify and ensure proper follow-up of individuals with potentially dangerous blood pressure elevation. Participants may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment, even though the BP is below the escape thresholds.
- In addition to the random zero (RZ) measurements required for study data, additional non-RZ (standard mercury sphygmomanometer) measurements may be taken on a more frequent basis at the study clinician's discretion to ensure participant safety.
- In particular, the PREMIER escape limits reflect the fact that although persons with Stage 1 hypertension (SBP 140-159 and/or DBP 90-95) are eligible for PREMIER, persons with Stage 1 hypertension 6 months after randomization should be referred to their personal MD for possible treatment with medication.
- If escape levels are reached, a BP Escape Tracking Record (Form #32, 83, 84, or 52) is filled out. The original is placed in the participant's chart at the site, and a copy is sent to the CC.
- If the participant requires a physician's evaluation and does not have a personal physician, qualified personnel at the clinical center will make a referral.

PREMIER Blood Pressure Escape Criteria

The following blood pressure escape levels and protocols have been established to ensure that participants are offered appropriate evaluation and therapy when clinically indicated. The actions taken when these escape levels are reached vary somewhat for screening and intervention. Participants may be referred for evaluation at any time if a qualified clinician believes such action is appropriate based on his or her own clinical judgment.

All escape blood pressures should be documented by completing the appropriate BP Escape Form (Form #32 for screening; #83 for 3-month, #84 for 12-month, and #52 for 6 and 18 month visits).

In the event that a randomized participant is referred to a clinician for evaluation, the clinical center should try to obtain four sets of end-of-intervention blood pressure measurements prior to treatment. Blood pressure measurements used to define and confirm escape may be used as end-of-intervention measurements, regardless of spacing. Care should be taken, however, that this

does not delay or otherwise interfere with appropriate clinical care. Regardless of the outcome of the referral, if possible all participants continue in the trial and get all study measurements.

Screening (Prior to randomization)

Escape Level #1:	The mean blood pressure recorded at any single visit, including PSV, SV1, SV2, SV3 or the 4th Baseline Blood Pressure, is SBP ≥ 180 or DBP ≥ 110 mm Hg.
Action:	Participant is excluded immediately and referred to a physician for further evaluation within one week.
Escape Level #2:	The mean cumulative blood pressure recorded at SV1, SV2, or SV3 exceeds the established upper limit of eligibility (see Protocol, section 6, Table 3).
Action:	Participant is excluded and referred to a physician for further evaluation within one month.

Intervention Period: 3-Month Visit

Escape Level #1:	The mean blood pressure recorded at the three-month visit is SBP ≥ 160 or DBP ≥ 100 mm Hg.
Action:	One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is SBP ≥180 or DBP ≥110, participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is SBP ≥160 or DBP ≥100, then the participant is referred to his/her personal physician for further evaluation within one month.

Intervention Period: 6-Month and 18-Month Visit Clusters

Escape Level #1:	The mean blood pressure recorded at any single visit is SBP ≥ 160 or DBP ≥ 100 mm Hg.
Action:	One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is SBP ≥180 or DBP ≥110, participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is SBP ≥160 or DBP≥ 100, then the participant is referred to his/her personal physician for further evaluation within one month.

Escape Level #2:	The cumulative mean blood pressure recorded at the end of the six or 18 month cluster of visits is SBP $\geq$ 140 or DBP $\geq$ 90 mm Hg.
Action:	Participant is referred to his/her personal physician for further evaluation within two months.

Intervention Period: 12-Month Visit

Escape Level #1:	The mean blood pressure recorded at the 12-month visit is SBP $\geq$ 160 or DBP $\geq$ 100 mm Hg.
Action:	One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is SBP $\geq$ 180 or DBP $\geq$ 110, participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is SBP ≥ 160 or DBP $\geq$100, then the participant is referred to his/her personal physician for further evaluation within one month. If the cumulative mean from the two visits is SBP ≥ 140 or DBP ≥ 90, participant is referred to a physician for further evaluation within two months.

Escape Level #2:	The mean blood pressure recorded at the 12-month visit is SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg.
Action:	One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is SBP ≥ 160 or DBP ≥ 100, then the participant is referred to his/her personal physician for further evaluation within one month. If the cumulative mean from the two visits is SBP ≥ 140 or DBP ≥ 90, participant is referred to a physician for further evaluation within two months.

As information about referrals for blood pressure escape levels is requested by the DSMB, staff are requested to make at least 3 attempts to reach the participant to determine the resolution of the referral.

Morbid Events Affecting Blood Pressure

Participants who suffer a cardiovascular event with a lasting effect on blood pressure (e.g., myocardial infarction, stroke) may continue with the interventions and follow-up clinic visits with the approval of their primary physician and a study clinician. Such events will be detected through the Follow-up Symptoms Questionnaire (Form #78) or the Follow-up Rose Angina

Questionnaire Form (#7). Follow-up of these events will be monitored via the Adverse Events Form (#30). Whenever staff become aware that such an event has occurred, they should immediately report it to the study clinician. If necessary, permission to continue from both the participant's personal physician and a study clinician should be documented in the participant's chart on the Adverse Events Form, with a copy sent to the coordinating center.

Participants complete a Baseline Rose Angina Questionnaire at SV1 and a Follow-up Rose Angina Questionnaire at 3, 6, 12, and 18 months.

At baseline, participants with a positive Rose Angina Questionnaire (Form #6, question #8 answered "positive") must be referred to a personal physician for evaluation and cannot participate unless approved to do so by both the personal physician and a study clinician. The participant's personal physician will be asked to confirm that the participant has had a negative exercise stress test within the last 6 months (defined as 6 months prior to the date the physician contacts PREMIER with the information), and that the physician approves of the patient participating in the PREMIER interventions. A study clinician must review the study chart and also agree that the participant may continue in the study.

At 3, 6, and 12 months, individuals with a positive Rose Angina Questionnaire are immediately referred to their personal physician for evaluation.

If **all prior** Rose Angina Questionnaires were **negative**, the participant is asked to refrain from further exercise until they have a stress test, and approval from both their personal physician and a PREMIER clinician.

If **any prior** Rose Angina Questionnaire was **positive**, the participant is asked to refrain from further exercise until they have approval from both their personal physician and a PREMIERclinician. A repeat stress test is not automatically required in this case; the decision to perform one is left to the discretion of the participant's personal physician. If the participant does not have a personal physician, she is given a referral to a physician whom she is advised to consult.

In either case, if angina is confirmed, they are advised to follow their physician's advice regarding exercise. Otherwise, they can restart exercise per PREMIER recommendations. In cases of physician-confirmed angina, an AE Form (#30) is completed.

At 18 months, individuals with a positive Rose Angina Questionnaire are immediately referred to their personal physician for evaluation and advised to follow that physician's advice regarding further exercise. Since the intervention is completed, the need for study clinician review is now moot. If the participant does not have a personal physician, a recommendation regarding further exercise may be made by a study clinician. However, the participant is also given a referral to a physician whom they are advised to consult. In cases of physician-confirmed angina, an AE Form (#30) is completed.

Hyperlipidemia and the Use of Lipid Lowering Medications

Hyperlipidemia is not an exclusionary criterion. However, lipid values outside of normal ranges are flagged for the participant, and a local clinician reviews these results and makes recommendations for referral as appropriate based on National Cholesterol Education Program (NCEP) guidelines. Participants who are placed on lipid lowering drugs, whether before or after randomization, may continue in PREMIER.

NCEP Guidelines for Treatment Decisions Based on LDL-Cholesterol

Dietary Therapy

	Initiation Level	*LDL Goal*
Without CHD and with fewer than 2 risk factors	$\geq$ 160 mg/dL	< 160 mg/dL
Without CHD and with 2 or more risk factors	$\geq$ 130 mg/dL	< 130 mg/dL
With CHD	> 100 mg/dL	$\leq$ 100 mg/dL

Drug Treatment

	Initiation Level	*LDL Goal*
Without CHD and with fewer than 2 risk factors	$\geq$ 190 mg/dL*	< 160 mg/dL
Without CHD and with 2 or more risk factors	$\geq$ 160 mg/dL	< 130 mg/dL
With CHD	> 130 mg/dL**	$\leq$ 100 mg/dL

* In men under 35 years of age and premenopausal women with LDL-cholesterol levels 190-219 mg/dL, drug therapy should be delayed except in high-risk patients such as those with diabetes.

** In CHD patients with LDL-cholesterol levels 100-129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment.

Laboratory evidence of diabetes or renal insufficiency

Participants who are excluded because of previously undetected diabetes or renal insufficiency are informed that this lab abnormality is potentially clinically significant and are encouraged to discuss the test result with their physician. Written documentation of the laboratory result is provided to the participant.

Other laboratory abnormalities

Participants receive copies of clinically relevant local and central lab results and are encouraged to share these data with their personal physicians. The central lab notifies sites immediately when an alert value is reached. In addition, a local clinician reviews all laboratory measurements and makes recommendations for referral as appropriate prior to sharing these laboratory measurements with the participants. If urgent referral is indicated, the participant will be informed and referred as soon as possible. Otherwise, local lab reports are provided to the participant to review with the personal physician at the participant's discretion.

The mere occurrence of an abnormal laboratory measurement is not considered to be an adverse event. Such measurements only trigger an AE form if the participant reports a diagnosis made by a health-care professional on the basis of the abnormal result. This report by the participant is

done through the completion of the Follow-up Symptoms Questionnaire Form (#78). Discussion of PREMIER laboratory measurements with ones physician as part of a routine clinic visit is not considered an adverse event.

Pregnancy and Other Exclusions

If a participant becomes pregnant during the study, she is excluded immediately from further participation in all study activities and her data are considered censored as of the date of conception, which is measured based on self-report. If she has not yet seen a physician, she is immediately referred for standard prenatal care. If a participant develops any other exclusionary condition (e.g., cancer) following randomization, further participation is determined by a study clinician in conjunction with the participant's personal physician.

Symptoms and Adverse Events (AE) Surveillance

The Follow-Up Symptoms Questionnaire (Form #78) is administered at the 3, 6, 12 and 18 month follow-up visits. A separate Baseline Symptoms Questionnaire (Form #16) is administered at SV3. Participants are specifically queried about gastrointestinal, musculoskeletal, and cardiovascular symptoms. Questionnaire responses are reviewed by study clinicians and referred for additional care as needed.

Participants are also queried using Form #78 at the 3, 6, 12 and 18-month follow-up visits about possible adverse events (defined below). Positive responses trigger an Adverse Events Form (#30), which is completed by an unblinded study clinician at the local site and then reviewed by a clinician at the coordinating center and classified as either gastrointestinal, cardiovascular, musculoskeletal, or "other" in nature. This information is then reported to the DSMB by site and treatment arm. Similar information reported by participants at other times (e.g., during intervention classes) is noted on the Safety Review Form (#31) and followed up with as needed to assure participant safety. To avoid possible reporting bias, such events do not constitute AEs unless they are reported at the regularly scheduled clinic visits.

The following constitute adverse events (AEs): heart attack, stroke, transient ischemic attack, heart failure, coronary angioplasty or bypass surgery, angina pectoris, broken bone, torn ligament, or any other serious injury to the bone or muscle. Evidence of the occurrence of these events is based on participant self-report that a health care professional has diagnosed the condition (Ques 15 on Form #78), and no attempt is made to verify the diagnosis. Physician confirmed angina following a positive Rose Angina Questionnaire also constitutes an adverse event and triggers the completion of Form #30.

Cancer, gallbladder disease, hyperlipidemia and diabetes are not considered AE's in PREMIER, but are tabulated and reported to the DSMB in a separate table.

All other outcomes that may be construed as being an adverse consequence of study participation, such as an injury while performing a study measurement, are documented on Form #31, reviewed, and followed up on as needed by a study clinician.

At all times, the paramount concern is the safety of the participant. If a symptom or AE seems likely to lead to termination of participation in the intervention, to the extent possible staff should collect end-of-intervention measurements before termination, giving highest priority to the four end-of-intervention blood pressure measurements.

Review of a participant's medical record to confirm adverse events is not required and should not be done. However, during the course of a medical record review for some other purpose a staff member may find evidence of a previously unreported adverse event. In this case, a Safety Review Form (#31) should be completed and reviewed locally to determine if the condition should affect the participant's further involvement in the study.

Musculoskeletal Injuries

Questions on the Prescreen Eligibility Form (#1) determine whether the participant has orthopedic or rheumatologic problems that might limit his/her ability to participate in the physical activity component of the intervention. Potential problems are reviewed by the PI or interventionist to determine whether the problem would make participation in the physical activity component of PREMIER unsafe. Once they are randomized, participants in Groups B and C are taught techniques for stretching, warm-up, and cool-down as a component of the intervention to reduce risk of musculoskeletal injuries. Musculoskeletal symptoms or injuries are reported on the Follow-up Symptoms Questionnaire (Form #78) or the Safety Review Form (#31). Severe or potentially clinically significant symptoms are brought to the attention of a PREMIER clinician who determines 1) if the physical activity portion of the intervention should be terminated either permanently or pending a clinical evaluation; and 2) whether referral for further evaluation or treatment is warranted. In some situations where there are musculoskeletal symptoms, or an injury has occurred, it may be appropriate for the interventionist to advise the participant on adapting his/her physical activity program. (For example, an individual who has sustained a leg injury may be advised about alternatives to walking.) An unblinded clinician is available to advise the interventionists.

If a musculoskeletal injury seems likely to lead to termination of participation in the intervention, to the extent possible staff collect end-of-intervention measurements before termination, giving highest priority to the four end-of-intervention blood pressure measurements.

Treadmill Testing

If a pre-exercise heart rate is <40 or >110 beats/minute, the study clinician is contacted and reviews the situation focusing on participant safety. The participant is not necessarily ill, and might still be a candidate for the test. The study clinician has the following options:

1. If the clinician determines that the abnormal heart rate is not pathological (e.g., a very slow rate in a trained athlete), the participant may perform the test as scheduled

2. If the clinician determines that the abnormal heart rate is not pathological but that the test would be safer if performed when heart rate is in the normal range, the participant will be asked to reschedule the test for a later time (later that day or on another day) when the participant's heart rate is within the acceptable range
3. If a reason for the slow or fast pulse is not self-evident and is potentially of concern, the study clinician may advise the participant to seek a medical evaluation. Treadmill will be performed only with MD permission after that evaluation.

If any criteria for discontinuing the treadmill test early are met (see Chapter 18, Fitness), examiners must proceed directly to the cool down stage of the procedure. If the test is discontinued because a participant is experiencing chest pain, the cool down procedure is accelerated by slowing the treadmill as rapidly as possible so that participants can dismount safely and staff can attend to their symptoms.

Data and Safety Monitoring Board (DSMB)

The DSMB provides independent oversight of safety monitoring. Clinical centers send copies of all AE forms to the Coordinating Center, where an unblinded clinician reviews the data and adjudicates the nature and severity of the event for reporting to the DSMB. AEs are classified as being either cardiovascular (cardiac or cerebrovascular), musculoskeletal, gastrointestinal, or other in nature, and this information is reported in aggregate to the DSMB, broken down by site and intervention arm. Symptom data from Form #78 are reported separately. The DSMB reviews safety data annually and can recommend that NHLBI terminate the trial early if participants are being subjected to undue risk or if the trial's objectives are met and further follow-up would serve no added scientific purpose.

The NIH "Guidance on Reporting Adverse Events to Institutional Review Boards" of June, 1999, requires all multi-site clinical trials with a DSMB to forward summary reports of Adverse Events to each IRB associated with the trial. Each summary report includes:

- A statement that a DSMB review of data and outcomes across all centers took place, and the date of the review
- A summary of the DSMB review of the cumulative adverse events reports from all participating sites without specific disclosure by treatment arm, unless safety considerations require such disclosure, or a statement indicating that no adverse events were reported from participating sites
- The DSMB's conclusion with respect to progress or need for modification of the protocol.

These summary reports are in addition to all other adverse event reporting procedures required by NHLBI, the trial protocol, each organization, and each local IRB, and are distributed to each Principal Investigator by the Coordinating Center within 30 days after each DSMB meeting. Principal Investigators are required to forward Summary Reports of Adverse Events to their local IRBs.

Local oversight

Originals of all AE forms remain stored at the clinical site, while copies are sent to the CC for review. The coordinating center annually sends a summary of adverse events to each site for distribution to that institution's IRB as required by local regulations.

24. STUDY OUTCOMES AND ADJUDICATION 3

Summary of Edits

24. Study Outcomes and Adjudication

In the event that Protocol rules relating to censoring and outcome determination do not clearly apply in a specific case, an Adjudication Committee reviews blinded individual participant data and makes a final resolution. This committee is comprised of study investigators and includes at least two clinicians and one statistician. The coordinating center tracks the activities of the Adjudication Committee and the outcome of its deliberations, and regularly reports back to the Steering Committee and DSMB.

Examples of issues that are likely to come to the Adjudication Committee include (but are not limited to) the following:

1. Blood pressure measurements are obtained outside the recommended time windows.

   Although the Steering Committee voted not to exclude measurements just because they exceeded predetermined windows of acceptability, practical considerations may complicate the interpretation of such measurements. For instance, if the first follow-up blood pressure for a participant occurs at six months post randomization, should this really be treated as a three month blood pressure or should the three-month measurement be left missing and the observed measurement used as the first of the four six-month measurements? As noted in chapters 12 through 15, target and acceptable windows exist for all study measurements, and all observations falling outside of the acceptable windows are deferred to the Adjudication Committee for final consideration.

2. Intermittent use of blood pressure lowering medication.

   Participants who are regularly taking antihypertensive medication(s) at the time of outcome assessment are classified as hypertensive and their BP data are considered censored at that time. If the use of antihypertensive medication(s) is intermittent, however, or if the participant had used such medications in the past but is not currently taking them, the case is referred to the Adjudication Committee to decide how to classify the participant in terms of hypertensive status and whether the BP measurements need to be censored.

3. Use of blood pressure lowering medication for reasons other than high blood pressure.

   Occasionally a participant will be taking blood pressure lowering medications for reasons other than high blood pressure. For example, a participant may be advised to take a peripheral alpha antagonist (such as doxazosin, terazosin, trimazosin) for benign prostatic hypertrophy (BPH). If these medications are being taken on a regular basis, the participant's blood pressure measurements are censored at the time the medication was started. If use of such medications is irregular, or if they had been used in the past and since discontinued, the Adjudication Committee determines whether the measurements

still need to be censored. In both cases, the Adjudication Committee determines the participant's hypertension status based on BP measurements obtained prior to starting this medication and any additional clinical information the committee chooses to obtain.

4. Exclusionary medications started after randomization.

Certain outcomes are censored as a result of starting exclusionary medications after randomization:

Medication	**Censored outcomes**
Insulin	Blood glucose, insulin
Oral diabetes meds	Blood glucose, insulin
Antihypertensive meds	Measured BP (hypertension status = HTN)
Oral steroids	BP, blood glucose, insulin. *(If BP is censored, hypertension status is based on BP measurements prior to start of the medication.)*
Oral breathing meds (other than inhalers)	BP *(If BP is censored, hypertension status is based on BP measurements prior to start of the medication.)*
Weight loss meds	All clinical outcomes

The Adjudication Committee does <u>not</u> need to review individual participant records if they are clearly taking an exclusionary medication on a daily basis and the above censoring rules apply. However, if use of exclusionary medication is intermittent or irregular, the Adjudication Committee reviews the individual case and decides if/what/when censoring should occur.

5. Cardiovascular Events

Persons may experience clinical events (MI or stroke) that affect blood pressure. In general, such events will not be considered as indicating hypertension. Blood pressure obtained during follow-up will be used in the analysis as long as the person remains off medications that influence BP. Still, there may be circumstances in which censoring may be appropriate.

Summary Edits

25. Data Management

This chapter outlines the responsibilities of the Clinic Coordinator, data coordinator, and/or data entry technician at each site with regard to data management. In addition to this chapter, information is also available in the user's manuals for the various data entry and data management systems, as well as in the two training slide shows that are posted on the PREMIER web site.

Staff ID's

All PREMIER staff must have a PREMIER staff ID number. To obtain a staff ID number, the Clinic Coordinator should e-mail the Project Secretary at the Coordinating Center with the following information:

- First and last name
- Project job title
- Address (work)
- Phone number (work)
- Fax number (work)
- E-mail address (work)
- Whether or not the staff person will require access to the PREMIER web site

The Coordinating Center will assign a new number within 24 hours of receipt of this information. Web site access will be set up within 7 days.

Quality Control Methods Prior to Data Entry

The Clinic Coordinator will need to manually employ the quality control methods outlined below in real-time before the participant leaves the intervention site for both the batch-entered and centrally entered data. These methods include:

Patient identification and record linkages. The ID in each form needs to be checked for transposition errors. The format must be "aaaaa#####." The initial 3 alpha characters must be the same as the first three letters of the participant's last name. The next 2 alpha characters must be the same as the first two letters of the participant's first name. The last five digits are unique identifying numbers for that participant. Each page of multi-page forms must have the same ID number. ID labels can be generated after each screening visit, before run-in and before each intervention period to help assure accuracy (refer to PREMIER Data Entry System User's Manual for further details on patient identification).

Legibility. All data must be checked for illegible handwritten replies, spelling errors, etc. All checked response boxes must have checks within designated spaces. Check to be sure that the forms are filled out in pen. Forms filled out in pencil are often difficult to read.

Form admissibility. All forms must be checked to determine if the form was completed within the specified time window. All forms must be checked to assure that the completed form is the correct one for the indicated visit or activity.

Missing information. All forms must be checked for unanswered items or sections of an otherwise completed form. The Clinic Coordinator must assure that all necessary forms have been completed for the indicated visit or activity before entry of the individuals visit data can begin. There are a few forms that are allowed to have missing data (patient history, psychosocial forms). This is indicated in the coding instructions for these forms. All other PREMIER data collection forms must be complete prior to data entry.

Consistency. All data must be checked to assure that information supplied in one section is consistent with data in another section of the same form. All forms for the same participant for a given visit must be checked to assure consistency. Skip patterns on forms should be checked for the correct data flow.

Range and inadmissible codes. All data must be checked to assure they do not contain values either outside specified ranges or undefined alphabetic or numeric codes.

The individual coding instructions that are attached to the relevant forms provide detailed instructions for coding and review procedures for each study form. Be sure to review the coding instructions for the form before completing the review process. See the section below for details on how to correct errors on the forms.

Data Edits on Forms

It is important to use the following process when making corrections to study forms to assure the accuracy and validity of the data.

- Participant responses should never be obliterated.
- A single slash should be made through the incorrect response and the correct response written next to it.
- The reviewer's initials, date of correction and an explanation of the edit should be written next to the data field that is being edited.

For example:

~~92~~ **90** *RL 8/5/99 Addition error*

If a participant makes a correction to a form, the Clinic Coordinator should

- Verify that the response is clearly written.
- Make a single slash through the old response.

- The reviewer's initials, date of correction and the notation "participant correction" should be written next to the data field.

For example:

YES	NO	
☒	☒	RL 8/5/99 participant correction

Data Entry

All forms will be batch entered by a PREMIER certified data entry technician. Range and logic checks are built into the system to try to deal with form discrepancies before entry. The data entry technician should enter the data as is from the form. The values not meeting the defined range and logic check criteria normally can not be entered. For some fields, it may be possible to override these checks. See the data entry user's manual for information on overrides.

The goal for data entry is to be current within two weeks in order for reports to be accurate.

Data Entry Flow

All data collection forms for a visit should be entered before the corresponding visit/flow forms. All forms including the visit/flow forms should be entered before any closeout forms.

For example: You just finished SV1 for a participant. The participant was eligible after the visit, but called up a day later and refused to continue.

1. Enter the BP form
2. Enter the Rose Questionnaires
3. Enter the Eligibility Questionnaire
4. Enter the SV1 Visit Form
5. Enter a Participant Closeout Form

The only exception to this is the series of forms collected prior to randomization that do not have to be entered prior to randomization (#20, 21, 23, 24, 25, 26, 27, 45, 46, 47, 48, 49). These forms must be collected/completed prior to randomization, but they do not have to be entered prior to randomization. However, it is recommended that the forms be entered prior to randomization whenever possible.

Quality Control Methods Following Data Entry

As the data entry technician enters the data, any values that do not pass the range or logic checks defined by the system will trigger a prompt to the data entry technician to confirm that it was

correctly entered. If it is not a data entry error and the technician confirms that it is entered as coded, the form will be rejected. At this point the technician can either flag the form for review, or in some cases, the override function can be used to enter the values as is.

Data Edits to Database

Most corrections can be made at the sites using the data edit feature in the PREMIER Data Entry System. See the Data Entry User's Manual and the Data Management User's Manual for details on these processes. Certain types of corrections will need to be made by the Coordinating Center due to potential conflicts in the data fields (e.g. a participant was closed out in error).

To have a correction made by the Coordinating Center, send an e-mail or fax to the Data Manager at the Coordinating Center with the participant ID, the name of the form, the date on the form, the data field in error and an explanation of the correction. For complex forms/edits, fax a copy of the form along with the request. The Coordinating Center will make the change and send an e-mail confirmation that the change has occurred. The Clinic Coordinator should also make these changes on the relevant participant data form (see "Data Edits of Forms" section above).

Data Validation

The primary measures of data integrity rely on the verification of data. Verification is a comparison of data before a transition (data entry) to the result after the transition to assure a one-to-one correspondence and assure that the transition process was "true". In order to assure the accuracy of the PREMIER data, the Coordinating Center has set up a two step process. 1) Validation of the data by the Coordinating Center completed at the end of each cohort and as a part of a site visit. 2) Validation completed by the individual sites.

Data Validation at the CC

Data validation will be done by the Coordinating Center to assure validity of the data. The Coordinating Center will request the following at the end of each cohort:

- All Blood Pressure forms for randomized participants
- Three charts chosen at random from randomized participants. This includes all clinical and intervention forms entered into the PREMIER data entry system.

Additional validation will occur as a part of site visits. The Coordinating Center will request a random set of forms (from both randomized and non-randomized participants), as well as three random charts from each site.

The site should copy the requested forms and complete the accompanying shipping log (form #36) and send to the Data Clerk at the Coordinating Center. A summary error report and a detailed error report will be compiled for the site. The Clinic Coordinator at the site and the Data

Clerk and Data Manager at the Coordinating Center will then work together to solve any discrepancies that may have occurred. The Clinic Coordinator is responsible for seeing that corrections are made to the forms if needed (see data edits on forms section). Corrected copies of the forms should be faxed or mailed to the Coordinating Center. Changes that need to be made to the database should be clearly noted on the form. The Coordinating Center will file all copies of the forms in the Coordinating Center's participant chart.

Data Validation by the Site

The Data Management system has several data validation reports available for the sites to validate their own forms. There are reports to view all screening data and all blood pressure data for randomized participants. There is also a report to print all intervention data that is located in the Intervention system. Unblinded staff can only access this report.

Sites also have the option of printing data for specific forms one participant at a time using the view data feature in the Data Entry system.

The following list is a guideline for the amount of data validation to be conducted at the individual sites:

- All screening data for randomized participants
- A random sample of other forms for randomized participants

Archiving

A copy of each site's master database will be transferred nightly via phone lines from the site computer workstation to the coordinating center's file server. Archiving will occur automatically at the coordinating center, which will contain the previous day's data from the sites on-line and all historical data off-line. The historical data is easily obtained if restoration is needed. In addition, all data collection forms need to be archived for the life of the study in hard-copy form so that copies may be sent to the coordinating center as needed for data management. Requests for copies of archived data will be made on a form-by-form basis by the Coordinating Center.

Use of PREMIER Computing Equipment

Kaiser Permanente Center for Health Research (CHR), as PREMIER Coordinating Center, is supplying the following equipment for use by PREMIER Study intervention sites:

- 1 Compaq Deskpro EN 6266
- 1 Lexmark Optra S1855
- 1 APC Universal Power Supply
- All Required peripherals, batteries, cables, and connectors

CHR retains rights of ownership for this equipment and all installed software. The equipment and software are provided for the sole purpose of conducting PREMIER activities as specified in the PREMIER Manual of Procedures (MOP). These activities include, but are not limited to, study communications, data entry, data transfer, reporting, data edits, and data repairs. This equipment will be returned to the CHR upon demand.

Additional uses or modifications of the equipment, software, and/or configuration, are not authorized, except as approved by the Coordinating Center Data Manager, and are considered a violation of study procedures. Non-authorized use or modification include but are not limited to: personal use of equipment or software, making and/or distributing unlicensed copies of PREMIER study software, installing additional software, making configuration changes to equipment or existing software, or connection to non-study networks.

Prior to action, the PREMIER Coordinating Center Data Manager must authorize any request for exceptions to this policy.

Other PREMIER Technical Manuals

Please refer to the following manuals for technical details/instruction.

- General Instructions for the PREMIER Workstation
- PREMIER Data Entry System User's Manual
- PREMIER Data Management System User's Manual
- PREMIER Intervention System User's Manual
- PREMIER Lab Tracking System User's Manual
- PREMIER Certification System User's Manual

These manuals should be filed in the "Computer Workstation User's Manual" binder supplied by the Coordinating Center. The manual should be updated with any revised manuals shipped by the Coordinating Center. The binder should be located near the site computer workstation for easy access by staff.

Summary of Edits

26. Trial Monitoring Reports

Introduction

During the trial's course, the Coordinating Center produces a variety of reports summarizing the characteristics of the study as a whole and of individual clinical centers. These reports are distributed to the members of the Steering Committee, to appropriate subcommittees, and to the Data Safety Monitor Board to monitor the progress of the trial. Selected reports are also available on a daily basis on the site workstations and on the PREMIER Web site.

Additional reports, produced for the DSMB only, permit the DSMB to monitor the efficacy and safety of the interventions. These reports include not only standardized reports issued at regular intervals but also ad hoc reports as requested.

The reports prepared for the Steering Committee focus on the recruitment of participants into the trial. These reports allow the Steering Committee to ensure that recruitment is proceeding in a timely manner and to identify potential recruitment problems at an early enough stage that they can be corrected. In addition, the Steering Committee also receives reports summarizing the completeness and quality of the study database.

The other committees receive reports relevant to their areas of expertise.

Current versions of the standardized reports can also be generated on demand using the file servers and on the PREMIER web site. This allows individual sites to get up-to-the-minute reports, further enhancing data quality.

Types of Reports

Recruitment/Follow-up Reports

Recruitment and follow-up reports summarize recruitment activity and follow-up to date. These reports assist field sites in meeting recruiting needs and in scheduling eligible participants for upcoming screening visits.

Baseline Data Reports

These reports compare the baseline characteristics of the randomized participants. Data are presented both by site and by treatment status. All of the information reflects baseline, pre-intervention data, and therefore should be comparable across treatment groups.

Quality Control Reports

Quality control reports include a number of reports related to the integrity of the PREMIER database and adherence to trial protocol by both participants and sites. These include digit preference reports and blood pressure protocol reports.

Laboratory QC and Results Reports

Laboratory quality control reports summarize lab tracking, including receipt, receipt status, and the collection of process measures such as start and stop times for 24-hour urine samples that will be used to establish the usability of data laboratory reports summarizing the results of laboratory analyses.

Side Effects Report

The side effects report summarizes side effects reported by PREMIER participants during the course of the study.

Outcome Measures and Safety Issues Reports

These reports are only sent to members of the DSMB. They comprise unblinded study data.

Data Management Reports

These reports summarize the data completeness and data quality for single site

Distribution of Reports

Monthly Steering Committee/Measurement Committee Reports

These reports are generally distributed 1-2 weeks prior to the meeting or conference call of each committee. Not every report is sent out in every mailing. The Coordinating Center reviews the available reports before each mailing and sends only those reports that have new and/or relevant data.

- Recruitment/Follow-up Reports
- Baseline Data Reports
- Quality Control Reports
- Laboratory QC and Results Reports
- Side Effects Report

Monthly Recruitment Committee Reports

The committee chair distributes these reports a week prior to the meeting or conference call.

- Recruitment/Follow-up Reports

Reports for DSMB Meetings

These reports are prepared and distributed about 2-4 weeks prior to each DSMB meeting.

- Recruitment/Follow-up Reports
- Baseline Data Reports
- Quality Control Reports
- Laboratory QC and Results Reports
- Side Effects Report
- Outcome Measures and Safety Issues Reports

Reports Available on Site Computer Workstation

These reports are available at all times and are run on the present 'live' data.

- Data Management Reports

Reports Available on the Project Web Site

These reports are available at all times and are updated weekly (recruitment) or monthly (other reports). They include selected reports from the following categories.

- Recruitment/Follow-up Reports
- Baseline Data Reports
- Quality Control Reports
- Laboratory QC and Results Reports
- Side Effects Report

Summary of Edits

27. Offsite Data Collection Visits

If randomized participants are unable or refuse to come to the clinical center, data collection can be performed at locations convenient for the participant. It is essential that staff try to have the data collection conducted in a quiet, private or semi-private room, where the required relaxed waiting time can occur before a random zero blood pressure measurement is taken, and where there is an interview setting that permits privacy.

In order to preserve blinding of the staff person measuring blood pressure, when the PAR is to be administered at an off-site data collection visit, two staff persons (one blinded and one unblinded) conduct the visit. If the PAR is conducted at this visit, the blinded staff person should not be present in the room.

The room should have a comfortable chair, and a table or desk so that the participant's arm can be at heart level. Check in advance that a table and chair are available, and that there is an uncarpeted area where the scale can be placed to measure weight. If necessary, staff may need to bring a card table and chair for the blood pressure measurement, and a sheet of hard plastic or wood to place under the scale. If blood samples are collected, they must be transported in a closed container with at least 2 latches, such as a tackle box or toolbox. Blood samples in vacutainers must be put into 2 plastic zip lock bags and transported inside the closed container.

Materials

- RZ or standard sphygmomanometer (see below)
- UC-300 portable scale
- Forms and questionnaires as needed for the visit
- Tape measure (if 6 or 18-month visit)

  if needed

- Table
- Chair
- Sheet of hard plastic or wood to place under portable scale
- Lab supplies for fasting blood draw and 24-hr urine sample
  1. Transport container with at least 2 latches
  2. Ice packs to cool samples
  3. A biohazard sign must be placed on the outside of the container.
  4. In addition to supplies for the blood draw listed in Chapter 21, the container must include:
     - ♦ Plastic zip lock bags
     - ♦ A spill kit including 10% bleach solution

- Plastic-backed "diapers" or barrier material to place under participant's arm during blood draw
- Biohazard bags for all potentially infectious materials
- Sharps containers for needle disposal

Conducting the visit

In general, blood pressure should be done before the other procedures.

1. Measure blood pressure
2. Measure weight

if 6 or 18-month visit, add:

3. Measure waist circumference
4. Complete visit questionnaires, including 7-day Physical Activity Recall (see below)
5. Review instructions for the 24-hour food recall
6. Draw blood
7. Give participant supplies and instructions for 24-hour urine

Measure blood pressure

Take the participant's blood pressure with the random zero sphygmomanometer using the procedures described in MOP Chapter 17 (Blood Pressure Assessment). If your institution or the participant's workplace prohibits the use of random-zero devices, a standard manometer can be used. If no device containing mercury can be used, you may use a standard anaeroid sphygmomanometer. When using a standard manometer, add 30 to the pulse obliteration point (POP) in order to determine the maximum inflation level (MIL).

Measure weight

Measure the participant's weight using the off-site visit protocol in Clinical MOP Chapter 20, Other Clinical Measurements.

Measure waist circumference

Measure the participant's waist circumference using the off-site visit protocol in Clinical MOP Chapter 20, Other Clinical Measurements.

Complete questionnaires

Encourage the participant to complete as many forms as possible. Unblinded staff certified in PAR techniques must administer the PAR.

Draw blood

Draw fasting blood sample using procedure in Clinical MOP Chapter 21, Central Laboratory Procedures. Place sample on ice in container and return to clinic for processing within 1 hour of collection of the sample.

Review instructions for 24-hour recall

Review instructions for the 24-hour food recall with the participant.

Review instructions for 24-hour urine

Review instructions for collection of the 24-hour urine sample with the participant. Make arrangements for delivery or pick up of the sample once collection is complete.

Review forms and conclude visit

Clinic staff review all forms before leaving the site.

Summary of Edits

28. Priorities for Collecting Follow-Up Measurements

Visit priorities

- If the choice is between obtaining one more six month visit and an 18-month visit, get the six month visit., and try again at 18 months.
- Home (or worksite) visits are an option (see Chapter 27, Offsite Data Collection Visits).
- Staff may be sent of town to complete visits in a remote location.
- The AASK trial is being conducted in 20 cities using RZ equipment with a virtually identical protocol. If needed, ask their help in obtaining BP measurements.

Participant transfers between sites

When participants transfer between sites, the following procedures should be observed:

1) Coordinator at the site of origin notifies the CC and the coordinator at the receiving site
2) Site of origin provides copies of records to receiving site using procedures approved by the sending site's IRB.
3) CC adjusts the data system to allow entry of forms at the new site, or makes arrangements for data entry of future forms.

Measurement priorities

1. *Blood Pressure* -- Blood pressure is the highest priority measurement and should be done before the other procedures. If possible, obtain a third Blood Pressure reading over any other measurement. You may opt for a lower priority measurement in place of a fourth Blood Pressure. If need be, obtain four Blood Pressure measurements in less time than allowed by window. Follow-up escape measurements may be used as regular outcome measurements, even if not within windows. However, subsequent measurements should be properly spaced.
2. *Weight*
3. *Medication use*
4. *Fasting blood specimens*
5. *Diet recall* -- The diet recall has priority over the 24-hour urine
6. *Fitness test* -- The fitness test is preferred over the PAR.
7. *PAR* -- The PAR can be administered over the telephone if the participant has a copy of the response prompts.
8. *24-hour urine*
9. *Psychosocial measures* -- Psychosocial measures can be self-administered, but are the lowest priority.