SECTION 8

OBSERVATIONAL STUDY

INTRODUCTION

A wide variety of important clinical and public health issues will be assessed with the Observational Study (OS). The most important purpose is the testing of new hypotheses with regard to risk of cancer, cardiovascular disease (heart disease and stroke), fractures and other major illnesses in post menopausal women. This will be achieved by relating information obtained on baseline characteristics to subsequent illness events and mortality. In addition, the gathering of biological specimens at baseline for storage and later analysis will allow etiologic hypotheses involving biomarkers to be examined in nested case-control or case-cohort studies.

The large size of the overall cohort (100,000), combined with the effort that is to be made to include sizable proportions of members of racial minorities, will permit the identification of risk factors for a number of the more common health outcomes in individual minority groups. Minority women have not been well represented in most past or present cohort studies of cardiovascular disease, cancer, or fractures. The OS can be expected to enroll almost 20,000 minority women as subjects. With these much greater numbers, it can begin to explore interracial differences in risk factors for conditions that occur with relatively high frequency, e.g., the major cancers, cardiovascular disease, and hip or forearm fractures.

Women who are interested in participating in the Women's Health Initiative (WHI) and who satisfy the OS eligibility criteria but who are not interested or eligible for the Clinical Trials (CTs) may be invited to participate in the OS. The OS has no intervention arm. Women may enter the OS during or between any of the three screening visits, although the majority are expected to enter at Screening Visit 1 (SV1).

Data on the OS participants will be obtained from questions they answer and from physical examinations and laboratory tests. Women in the OS will complete the same baseline questionnaires as the CT participants. Women in the OS will also complete a supplemental OS questionnaire at the time of enrollment. The supplemental questionnaire will obtain additional information about exposures and risk factors relating to the epidemiology of primary outcomes of the OS.

OS participants will be followed-up by means of annual self-administered mailed questionnaires. These questionnaires will ascertain updated information on hospitalization(s) and the occurrence of other outcomes of interest since the previous medical history update, changes in a few key exposure variables, and updated personal information (change in address, etc.).

At three years, all OS participants will complete a Clinical Center (CC) visit in addition to the follow-up questionnaires. The three-year visit will include physical measures and questionnaires.

8.1 Eligibility for the OS

Eligibility criteria for the OS are similar to the CT. However, some women who do not fulfill all the eligibility requirements for one or more arms of the CT will be eligible for the OS. Inclusion criteria for the OS include the following (see *Vol. 1 - Study Protocol and Policies, Section 1 - Protocol, Section 4.4 - Study Population* for eligibility and exclusion criteria):

- Female volunteers of all races and ethnicity, with or without a uterus or ovaries.
- Aged 50-79, inclusive, at the screening contact (*Form 2/3 - Eligibility Screen*).
- Postmenopausal, based on the Dietary Modification (DM) menopausal algorithm (see *Section 4.5.2 - Definition of Postmenopausal Status*).
- Likely to be residing in the study area for at least three years after study enrollment.
- Providing written informed consent.

Women who are ineligible for the OS are also ineligible for the entire WHI study. The following **exclusion criteria** apply to the OS (as well as the CT):

- Any medical condition associated with predicted survival of less than three years in the judgment of the CC physician (e.g., class IV congestive heart failure, obstructive lung disease requiring long-term ventilation or supplemental oxygen in the past, severe chronic liver disease with jaundice or ascites, kidney failure requiring dialysis, sickle cell anemia).
- Alcoholism.
- Other drug dependency.
- Mental illness, including severe depression.
- Dementia.
- Active participant in any other intervention trial where participants are individually randomized to an intervention or control group.

See *Vol. 5 - Data System, Appendix C.2 - Eligibility Criteria* for how each criterion is mapped to data on the questionnaires.

8.2 Inviting Women into the OS

8.2.1 Identifying OS Participants

Women who satisfy the eligibility criteria listed in *Section 8.1 - Eligibility for the OS*, may be enrolled in the OS. OS participants will be recruited from four sources:

1. All women who are found to be ineligible for the CT during the screening visits (SV1-SV3), but who satisfy the eligibility criteria for the OS, should be invited to enter the OS. This includes women who become ineligible between visits. When it becomes clear that the woman is ineligible for the CT, do not continue any procedures required by the CT. Enter all data collected up until this time, however, so that the reason for ineligibility is recorded in the database.

2. All women who are eligible for the CT (and hence also eligible for the OS) but who become uninterested in participating in either the Hormone Replacement Therapy (HRT) or the DM components of the CT during the screening visits (SV1-SV3) should be invited to enter OS. This includes women who become uninterested in the CT between visits. Do not continue CT procedures, but enter all data collected up until the time she became uninterested in the CT.

3. Some women who, during the screening process before SV1, are found to be eligible for the OS, but who are ineligible or uninterested in the CT, should be invited to participate in the OS. The number of such women invited into OS should be a sufficient number to meet the CC's enrollment target. These women should be scheduled for SV1.

4. Because of the approximately one year time lapse between the start of the CT and the start of the OS, Vanguard Clinical Centers (VCCs) may already have screened women who are either ineligible for the CT or unwilling to participate, but who are eligible and willing to participate in the OS. Vanguard Clinical Centers should review their screening records to identify potential OS participants falling into these categories. Potential OS participants identified from screening records may be recontacted and invited to participate in the OS.

8.2.2 Determining Eligibility for the OS

To determine eligibility for the OS, a woman must have completed *Form 2/3 - Eligibility Screen* and CC staff completed *Form 6 - Final Eligibility Assessment*. An eligibility determination for a woman can be made in WHILMA at anytime, and if appropriate, the woman may be invited into the OS if the minimum eligibility criteria are satisfied (age-eligible, post-menopausal, likely to reside in the area for three years and no exclusionary conditions).

8.2.3 Informed Consent for OS

Once a potential OS participant has been identified and has been found to meet the eligibility requirements outlined in *Section 8.1 - Eligibility for the OS*, she should be invited to participate in the OS. All OS participants are required to sign the OS Consent Form as part of the enrollment process. In addition, the Initial Consent Form should have been completed or should be completed at the beginning of SV1 (see *Section 4.2.4 - Guidelines of Activities*).

For women who enter the OS while at a CC visit, describe the nature of the study to her (see *Section 4.2.5.1 - OS Informed Consent* for suggested script). Give her a copy of the OS Consent Form and let her read it and ask any questions she has. Ask her to sign the OS Consent Form and give her a copy of the OS Consent Form for her records (see *Section 4.2.4.3 - Initial (Screening) Informed Consent* for a more detailed description of the OS informed consent procedures). *Form 11 - Consent Status* should be completed and data entered by CC staff when the consent form is signed or the participant refuses, to indicate the participant's consent status for eligibility and tracking purposes.

Clinical Centers may develop a consent form that combines all the elements of the Initial Consent Form and the OS Consent Form for women who come to SV1 specifically to enter the OS. (All changes to consent forms including the combining of Initial Consent with OS Consent require approval from the Project Office.) If a combined consent form is used, indicate on *Form 11 - Consent Status* that both Initial Consent and OS Consent have been obtained.

8.2.4 Entry Into OS Outside a CC Visit

Some women may become uninterested or ineligible for CT between SV1 and SV2 or between SV2 and SV3. For women who have completed the OS tasks outlined under *Section 8.3.1 - Questionnaires and Procedures Administered at a CC Visit* but become eligible for the OS between CC visits, entry into OS may occur outside a CC visit (CC option). Clinical Centers should develop procedures for mailed consent that are approved by their Institutional Review Board. The recommended procedure is to invite the woman to enroll in the OS by telephone (see *Figure 8.1* for sample telephone script) and then to mail her a packet containing: a cover letter, the "Welcome to the OS" handout, two consent forms (signed by the appropriate WHI CC signee), the self-administered questionnaires that she has not yet completed, the WHI magnet, optional health education materials (e.g., Breast Self-Exam [BSE] shower card, health pamphlets) and a self-addressed, stamped, return envelope. The cover letter should ask her to sign both consent forms, return the one with the questionnaires, and keep the other for her records. A sample cover letter is included in *Appendix E.6.1*.

The CCs should take into consideration each woman's language and reading ability in deciding whether or not the option of enrollment into OS outside a CC visit is appropriate.

8.3 Baseline Procedures for OS Participants

A woman must have completed all the required OS tasks to be enrolled into the OS. See *Vol. 5 - Data System, Appendix C.1 - List of Tasks Required for Randomization*.

All following questionnaires must be completed to determine eligibility:

Form 2/3 - Eligibility Screen

Form 6 - Final Eligibility Assessment

8.3.1 Questionnaires and Procedures Administered at a CC Visit

Certain tasks, outlined in this section, must be completed during a CC visit. If these tasks have not already been completed, they should be administered. If they cannot be completed during the visit at which a participant enrolls in the OS, she should be given a CC appointment to enable the completion of the outstanding CC visit tasks.

The procedures for the required OS CC tasks are identical to those for the CT, except for one change to blood draw procedures (see below).

The following questionnaires administered by CC staff during a CC visit are required on all OS participants:

Initial Consent (and *Form 11 - Consent Status* indicating Initial Consent has been signed.)

OS Consent (and *Form 11 - Consent Status* indicating Initial Consent has been signed.)

Form 43 - Hormone Use

Current Medications (direct data entry or *Form 44*)

Current Supplements (direct data entry or *Form 45*)

The following CC procedures are required on all OS participants:

Form 80 - Physical Measurements

Form 100 - Blood Collection and Processing. The procedures are almost identical to the CT; specifically, blood drawn for local lab analyses and for specimen repository are required for OS women. The local lab has a lower priority. Attempts should be made to collect the blood for McKesson Bioservices before collecting the local blood. It is important that **fasting** blood is obtained. If a woman is not fasting at the time of the clinic visit, she should be given another clinic appointment so that fasting blood can be obtained. At least 2 ml. of must be obtained for a participant to be eligible for OS enrollment. This means that a minimum of 4 ml. of blood must be drawn into a royal blue tube (to make 2 ml. of serum). Thus, at least two aliquots should be sent to McKesson Bioservices (1 ml. each in cryovial, 02 and 03).

The following additional CC procedures and questionnaires are required for OS participants at Bone Densitometry CCs:

Form 87 - Bone Density Scan

Form 101 - Urine Collection and Processing

In order to limit study costs and the burden on the participant and CC staff, baseline OS procedures and questionnaires that need to be done at a CC visit should be completed at SV1 if possible. OS participants do not need any further screening visits once the baseline CC requirements have been satisfied. Clinical Centers should try to keep the need for further CC visits to complete baseline OS procedures to a minimum by:

1. Completing the CC procedures and CC-administered questionnaires required for OS participants at SV1 and not assuming that procedures can be delayed until a subsequent screening visit.
2. Ensuring that women come to screening visits prepared for procedures. This means that they should be fasting (for fasting blood draw), dressed in suitable clothes (for physical measurements), and should be reminded to bring all medications and supplements (to enable the completion of *Task 44 - Current Medications* and *Task 45 - Current Supplements*).

The following CC tasks required for CT participants are **NOT required for OS participants**:

Form 39 - Cognitive Function

Form 81 - Pelvic Examination/Pap Smear (HRT)

Form 82 - Endometrial Aspiration (HRT)

Form 84 - Clinical Breast Exam

Form 85 - Mammogram

Form 86 - ECG

Form 90 - Functional Status

However, if any of these procedures have been completed before the participant enrolls in the OS, the information should be entered into WHILMA.

8.3.2 Self-Administered Questionnaires

The following self-administered questionnaires are required on all OS participants:

Initial Consent - (and *Form 11 - Consent Status* indicating that the OS Consent Form has been signed.)

OS Consent - (and *Form 11 - Consent Status* indicating that the OS Consent Form has been signed.)

Form 20 - Personal Information

Form 30 - Medical History

Form 31 - Reproductive History

Form 32 - Family History

Form 34 - Personal Habits

Form 37 - Thoughts and Feelings

Form 42 - Observational Study Questionnaire

Form 60 - Food Frequency Questionnaire (FFQ)

Self-administered questionnaires can be administered in several ways (or a combination of these):

1) Mailed before SV1 to be completed at home and returned at SV1. This option can not be used for *Form 37*.

2) They can be completed by the participant at the CC during the CC visit if time and space permit. This method is preferable so that the participant is able to ask the CC staff questions about any of the forms, and to ensure that questionnaires are completed and returned to the CC.

3) They may be given to a woman at a clinic visit to complete at home and mail back to the CC, or returned at the time of the next CC visit (if CC procedures are incomplete). Participants who are to complete the self-administered questionnaires at home should be provided a postage-paid, addressed envelope in

which to mail the questionnaires to the clinic, and should be given the name and phone number(s) of the CC staff member(s) to call with questions.

4) Women who have completed the CC visit procedures and questionnaires (see *Section 8.3.1 - Questionnaires and Procedures Administered at a CC Visit*), do not need to return to the CC to enroll in the OS. The self-administered questionnaires not yet complete may be mailed to the woman along with a cover letter including the name(s) and phone number(s) of CC staff members to call with questions and the return envelope. A sample cover letter is included in *Appendix E, Figure E.6.1* - As noted in *Section 8.2.4 - Entry Into OS Outside a CC Visit*, this packet would also include the OS Consent and other material.

See *Vol. 3 - Forms* for detailed instructions on completing each of the baseline forms.

The following questionnaires are **NOT required for OS participants**:

Form 4 - HRT Washout (HRT)

HRT Consent (HRT)

DM Consent (DM)

CaD Consent (CaD)

Form 53 - HRT Calendar (HRT)

Form 62 - Four-Day Food Record (4DFR) (DM)

However, if any of these questionnaires have been completed before the participant enrolls in the OS, the information should be entered into WHILMA.

8.3.3 Procedures for Questionnaires Not Returned to CC

Each CC should develop an approach that leads to the required collection of data from the women. The follow-up procedures should not be so aggressive that non-compliant women enter the OS. Suggested follow-up procedures include:

1. A postcard after one week to all women who were given questionnaires to return. The text on the postcard should have a combination thank you/reminder message (e.g., “thank you for returning the questionnaires” and “if you haven't returned them yet, please send them back soon”). A sample postcard is in *Appendix E, Figure E.6.2*.

2. A telephone call after three weeks to women who have not returned all forms. On this call, speak to the woman (rather than leave a message), ask her to complete and return the forms, and ask if she needs new forms mailed to her. Mail new forms if requested. For a sample telephone script see *Figure 8.2*.

8.3.4 Maximum Time for Completion of Baseline Data

For women whose SV1 is on or **after** September 1, 1994, all forms and procedures must be complete within six months after SV1 (excluding *Form 2/3 - Eligibility Screen*, and *Form 60 - FFQ*).

For women screened by VCCs **before** September 1, 1994, all forms and procedures must be completed within one year after their SV1 visit (excluding *Form 2/3 - Eligibility Screen*, and *Form 60 - FFQ*).

8.3.5 Quality Assurance Procedures

Quality assurance procedures associated with the OS forms and procedures are the same as those for the CT. Before the participant leaves the CC do a final check that she has signed the OS Consent, and that all baseline CC procedures have been completed. Review all completed self-administered questionnaires for completeness; if one or more pages are missing, return to the woman to complete. Do not return to the woman if it appears that she has purposely refused to answer questions of a sensitive nature. Forms mailed to the CC should be reviewed in the same manner with telephone callbacks to the woman when necessary to complete the information on the form.

8.3.6 Ending the OS Baseline Visit

Participants in the OS may be seen in the CC only once during screening and will not usually be seen again until three years after the baseline information is obtained. Thus, efforts to maintain their interest in WHI and ensure retention and follow-up will be very important. Before the end of the final OS baseline visit the participant should be given an outline (verbal and/or written) of what to expect and what will be requested of her during the course of the OS. Explain the importance of future participation. Make sure that the participant has a phone number for the CC. Ask her to notify the CC if she moves to a different address. For women enrolling outside a clinic visit, this information can be provided by mailed materials (cover letter, OS Consent, "Welcome to the OS" handout).

8.3.6.1 Annual Newsletters

Inform the participant that she will start receiving yearly newsletters within the next 12 months, and that they will arrive at about the same time each year. Tell her that the purpose of these newsletters will be to keep her informed of the progress of the study, and to verify her address through the post office.

These newsletters will be mailed to the CCC at six months post-enrollment, with the return address of each CC. It is the responsibility of the CC to update the database in the case of a change of address.

8.3.6.2 Yearly Update Questionnaires

Inform the participant that each year she will receive a few questionnaires from the CC, starting one year from the date that she enrolled in the study. Tell her to expect these questionnaires at the same time each year, about the time of the anniversary of her enrollment in the OS. Inform her that she should complete these questionnaires and mail them back to the CC in the enclosed pre-paid envelope as soon as possible after receiving them. Reassure the participant that completing the three yearly update questionnaires will be a lot less work than the baseline questionnaires, and outline what these questionnaires will be about.

- The medical history update questionnaire will ask the participant to report the occurrence of important medical problems such as hospitalization, heart attack and heart disease, stroke, cancer and fractures.
- The OS update questionnaire will ask for updated information on things such as hormone replacement therapy, which may affect her risk of developing certain medical conditions.

Every few years the participant will also receive a personal information sheet listing information such as her telephone number, address, and health care provider. She will be asked to update and return the sheet to the clinic if there are any changes to the personal information listed.

8.3.6.3 Future CC Visits

For CCs that are not Bone Densitometry CCs, inform the participant that she will be asked to return to the CC for a visit at the 3-year anniversary date. Explain to the participant that the procedures and measurements done at the 3-year CC visit will be similar to those done at the baseline CC visit(s). Before her visit, the CC will mail a packet of questionnaires for her to complete and bring to the visit. Procedures at the CC visit will include some physical measurements such as blood pressure and weight, and a blood sample will be drawn.

For Bone Densitometry CCs, inform the participant that she will be asked to return to the CC at 3, 6, and 9 years after her enrollment into the OS. OS participants attending one of the Bone Densitometry CCs will have their bone density measured at the follow-up visits and will be asked to provide a sample of urine, in addition to the other procedures (questionnaires and physical measurements).

8.3.6.4 Arranging Follow-Up for OS Participants

After the participant has completed the baseline questionnaires and procedures listed above, her baseline OS activities are completed. At this point, you should verify that her current address is accurate and she is not planning to move within the year. If she routinely is away at the time she would receive either the yearly newsletter or the yearly follow-up questionnaires, ask for that address as well. Thank her for her participation in the study. Explain to the participant that it is very important to obtain complete follow-up information on all participants in order to ensure that the results of the study are valid and scientific. Check that she has the CC's phone number. If the participant has not completed all the self-administered OS baseline questionnaires by the end of the OS Baseline CC Visit, check that she has a copy of each of the outstanding questionnaires and a return mailer. Advise her to contact the CC if she has questions concerning the completion of these questionnaires, and ask her to mail the completed questionnaires to the CC as soon as possible.

Provide the woman with the "Welcome to the OS" handout, the membership ID card, and the WHI magnet. The CCs have the option of also providing health education materials (e.g., BSE shower card, health pamphlets) as incentives.

8.3.7 Enrolling Women in the OS

When a woman has completed the OS Consent and all of the OS tasks, enroll her into the OS. To be enrolled, a woman must meet the eligibility requirements; *Form 2/3*, *Form 6*, and *Form 11* must be complete; and the woman must have completed all of the required forms and procedures listed in *Section 8.3.1 - Questionnaires and Procedures Administered at a CC Visit* and *Section 8.3.2 - Self-Administered Questionnaires*. To enroll a woman in the OS, invoke the enrollment function in WHILMA as described in *Vol. 5 - Data System, Section 6.3 - OS Enrollment*.

8.3.8 Reporting Abnormal Findings

Abnormal findings on blood pressure or CBC must be reported to the women and her physician or clinic. See *Sections 4.2.7.1 - Blood Analysis Results* and *9.2.6 - Alert Values* [for BP] for the procedures.

8.3.9 Baseline Procedures on Participants Who Have Completed Part of the Screening Process Before September 1994

At the start of the OS in September 1994, VCCs should give priority to recontacting women who have attended SV1 (with or without SV2 and SV3) before the start of the OS, but who did not enroll in the CT. All such women should be recontacted as soon as possible after the start of the OS and invited to participate in the OS (see *Figure 8.1* for sample telephone script). If the woman agrees to participate in the OS, efforts should be made to complete the outstanding baseline questionnaires and procedures within as short a time period as possible. (This urgency does not apply to participants who completed prescreening activities [or SV0s] but did not attend SV1 before the start of the OS.)

For women who have completed the CC visit tasks outlined in *Section 8.3.1 - Questionnaires and Procedures Administered at a CC Visit*, the procedures for entering these women are similar to those in *Section 8.2.4 - Entry Into OS Outside a CC Visit*. A sample cover letter for enrolling women who completed the screening process prior to 9/1/94 is in *Appendix E, Figure E.6.3*.

If a woman has not completed the CC visit tasks outlined in *Section 8.3.1 - Questionnaires and Procedures Administered at a CC Visit*, she should be invited for another CC visit to complete the remaining tasks. The procedures for entering these women are similar to those for other women entering the OS during a clinic visit.

In addition, for all women who completed self-administered questionnaires before September 1994, certain forms must be updated after September 1, 1994. These include *Form 2/3, Form 20, Form 30, Form 31, Form 32,* and *Form 34*. *Form 60* and *Form 37* do not need to be updated and should not be given to the woman unless she has never completed these forms. *Form 2/3* should be updated at the telephone call during which the woman is invited to enter the OS.

There are several ways to update the other forms depending on whether the old forms are still available or not, have been entered into the database or not, or are mark-sense forms or not. One option is to send new forms to the woman in the packet with the OS Consent and the questionnaires not yet completed by the woman. The instructions should state that even though she has already completed some of these questionnaires, we need her to fill them out again.

Another option for forms that have been entered into the database before a woman enrolls in the OS is to mail the actual forms the woman has **already completed** to the woman (in the packet with the OS Consent and other forms not yet completed). (The OMB number and text need not appear on the forms.) She should be asked to review these forms, make any changes with a red pen (which should be included in the packet) and return all forms with the OS Consent to the CC. (A post-it note on these forms saying "Use red pen" may be helpful.) After the old forms are returned, change the date on these forms to be the date the forms were returned to the CC, whether or not any changes were made by the women. Edit the new date and any changes into the database, when the forms are returned. This option is also best for mark-sense forms. They should be scanned before mailing them back to a woman if they have not been already.

Finally, for forms that are not mark-sense forms and that have not yet been entered into the database, the forms can be mailed to the woman to update (no red pen needed). Then after the date on the forms has been changed to be the date received by the clinic, the entire form can be entered into the database.

Whichever option is used, it may be helpful to send the woman a Questionnaire Description Sheet (*Appendix E, Figure E.6.4*). On this sheet, you can indicate which forms need to be completed and which need to be updated.

8.4 OS Measurement Precision Study - OS-MPS

The OS Measurement Precision Study (OS-MPS), as discussed in *Vol. 1 - Study Protocol & Policies*, will include a subsample of 1,000 women randomly selected from among new OS enrollees. The women chosen to participate in this study will be asked to repeat four of the questionnaires from the baseline CC visit approximately 10 weeks after OS enrollment and return to the CC in order to have their blood drawn. The OS-MPS will provide critical scientific data about the reproducibility of measures such as physical activity and reproductive history from the self-administered questionnaires, and will provide repeat fasting blood samples to test the accuracy of future blood measures.

8.4.1 Participants

One thousand women will be invited to participate in the OS-MPS from among women who enrolled in the OS during the period of September 1, 1996 to May 30, 1997. At each of the forty CCs, twenty-five participants will be randomly selected from among new OS enrollees to participate in this study. CCs should be sure to inform all OS participants enrolled during this time that there is the possibility they may be invited to participate in the OS Measurement Precision Study. This study is described in the model OS consent under "What Will You Be Doing?" The first list of participants selected for the OS-MPS will be identified on the *OS-MPS Participant Status Report* that will be mailed to CCs on or about October 15, 1996.

For each of the first five months of enrollment during the OS Measurement Precision study period, approximately five participants from each CC will be selected. Additional participants may be selected in the last four months of this period to account for non-response and variations in sampling. Please note that each CC is required to **enroll** into the OS-MPS twenty-five participants who complete the four questionnaires and have a blood draw. To meet this enrollment goal, the CCC will select more than twenty-five participants, depending upon the number of randomly selected women who decline to participate. The selection of OS-MPS participants will be stratified by both ethnicity and age.

8.4.2 Forms

The subset of questionnaires that each participant in the OS-MPS will be asked to repeat is determined by the group to which your particular CC has been randomly assigned (see list below). Each woman participating in the OS-MPS will repeat four of the questionnaires she completed during her screening visits and return to the CC to have her blood drawn.

The following lists specify the questionnaires and procedures that will be completed by the OS-MPS participants at the CCs assigned to Group A or Group B:

Group A:

Form 2 *- Eligibility Screen*
(selected questions; to be self-administered even if *Form 3* was used at baseline)

Form 30 *- Medical History Questionnaire*

Form 37 *- Thoughts and Feelings*

Form 42 *- Observational Study Questionnaire*

Form 100 *- Blood Collection and Processing*
(completed by CC Staff)

Group B:

Form 20 *- Personal Information* (selected questions)

Form 31 *- Reproductive History Questionnaire*

Form 32 *- Family History Questionnaire*

Form 34 *- Personal Habits Questionnaire*

Form 100 *- Blood Collection and Processing*
(completed by CC Staff)

The following are the CCs assigned to Groups A and B:

Group A CCs:

Atlanta
Boston
Bowman Gray
Buffalo
Chicago-Rush
Cincinnati
Gainesville
Honolulu
Houston
Iowa City
La Jolla
Los Angeles
Madison
Medlantic
New York
Pittsburgh
Portland
Tucson
UC Davis
Worcester

Group B CCs:

Birmingham
Chapel Hill
Chicago
Columbus
Detroit
GWU
Irvine
Memphis
Miami
Milwaukee
Minneapolis
Nevada
Newark
Oakland
Pawtucket
San Antonio
Seattle
Stanford
Stony Brook
Torrance

8.4.3 Procedures

The procedures for the OS-MPS are identical to those performed during the baseline CT and OS visits with two expections. First, failures or refusals for the blood draw are acceptable—the participant does not need to return for a repeated attempt to draw her blood. Second, all questionnaires must be completed before or at the CC visit scheduled for the OS-MPS blood draw. The questionnaires may not be sent home to be completed after the OS-MPS visit. At each CC, 20 of the 25 participants must complete the forms/blood charts; up to five may agree to complete only the required forms.

The following are the procedures to recruit women into the OS-MPS and to complete the study:

1. Beginning in October 1996, the CCC will send the *OS-MPS Participant Status Report* to each CC via the weekly FedEx. This report will list at least five OS-MPS participants who have been randomly selected from OS enrollees. This report will also serve as a dispositions record and needs to be mailed back to the CCC to update the status of all CC OS-MPS participants.

   Each month, the CCC will also supply the CCs with the necessary cover letters and forms, including Spanish forms and cover letters, if appropriate (based on the WHILMA "Spanish Flag"). Note that the CCC will include alternate versions of the cover letter to use for participants who only agree to complete the forms but not return for the blood draw (in addition to the full cover letter versions and questionnaires). A sample containing the text of the cover letter is given in *Figure 8.4 - OS-MPS Cover Letter*. If you prefer to mail participants the cover letter on your own stationary, use the electronic model letter emailed to the clinic managers on September 6, 1996.

   If you have a satellite clinic, the OS-MPS packet, for both will be mailed to the primary and satellite clinics, respectively.

   Additional packets of questionnaires will be provided by the CCC to allow for participants who forget to bring their completed questionnaires with them to the CC.

2. Over the course of the next four weeks, after receiving the list of participants, each CC will contact these participants by telephone to inform them of their selection and explain the purpose and procedures of the OS-MPS. Remind the participant that her participation is voluntary and that she has the right to decline without affecting her continued participation in the OS. Explain that the study includes repeating four questionnaires at home and returning to the CC for another fasting blood draw. Emphasize that we will gain important information about how reliable our questionnaires are (do not say ". . . how reliable your responses are"). For a sample telephone script, see *Figure 8.3*.

   For each woman who agrees to participate, schedule an appointment for a return visit to the CC for a date approximately 10 weeks (range: 8-15 weeks) after her enrollment in the OS. If a participant who has been selected to join the OS-MPS refuses to return to the CC for the repeat blood draw, you must still invite her to participate in the study by completing the questionnaires and mailing them back to the CC. The *OS-MPS Participant Status Report* will identify the date by which the visit must be completed.

3. Two weeks before her scheduled appointment, mail a packet that includes the questionnaires to be repeated and the appropriate cover letter (both furnished by the CCC).

   The questionnaires in the packets are identical to those completed during screening and before OS enrollment. The packet sent to participants from Group A CCs will contain a *Form 2* that has been marked (by the CCC) to exclude certain questions participants are not required to repeat. Similarly, Group B CCs will be sending out packets that contain a *Form 20* that has been marked (by the CCC) to exclude certain questions. All OS-MPS forms will be marked as a "non-routine" visit type by the CCC.

   Mail the packets of questionnaires to the participant **via first-class mail**. Include the following in the envelope:

- the standard cover letter -- write in the place, date, and time of the participant's appointment as well as the telephone number of the CC, sign the letter, and insert it into the packet

  For those participants who refuse to return to the CC for a blood draw, insert the alternate cover letter into the packet. Write in the telephone number of the CC and sign the letter. Add a stamped, self-addressed envelope in which she can return her questionnaires.

- the four questionnaires, and
- a No. 2 pencil to be used when filling out the mark-sense forms

4. The day before a participant's scheduled visit, call her to remind her of the visit time (optional) and to fast for 12 hours before the visit.

5. At the OS-MPS visit, do the fasting blood draw and collect the completed questionnaires. If the participant arrives without the completed questionnaires, ask her to fill out the questionnaires at the visit. The CCC will have sent extra packets of questionnaires to CCs for this purpose. If the participant says that she has already completed the forms but left them at home, you may give her a stamped, addressed envelope in which she can return her questionnaires. Ask her to mail the questionnaires within 24 hours of the visit.

   Review the questionnaires for completeness as you would have done during screening procedures. Refer to *WHI Manual - Vol. 2, Section 4 - Screening* and IRS #96-0198.

   The CC should follow-up on any participant who schedules a return visit to the CC and then fails to show up at the appointed time. Call these participants within 48 hours to reschedule an appointment for them. If a participant is unable or unwilling to make a return visit to the clinic, ask that she still participate in OS-MPS by filling out the packet of questionnaires and returning them to the CC by mail. Send her a stamped, self-addressed envelope in which she can return the completed questionnaires.

6. Thank the participant for the effort she has put into this study.

7. When completed forms are collected, check to make sure the visit type on all forms is marked as "non-routine" (including *Form 100 - Blood Collection and Processing*).

8. Collect and process the blood in the usual manner, including the local analyses of blood.

9. Enter the data into WHILMA in the usual manner. Note that the visit type should be "non-routine." For CCs in Group B, please note that data screens for *Form 20* will not be altered to remove the questions the women are asked not to answer. Care is advised during data entry of *Form 20*.

10. Record the disposition of each participant on the *OS-MPS Participant Status Report*, indicating if she had declined the blood draw, the forms completion, or both, when you have completed recording the disposition for each woman on the report, mail the report back to the CCC.

8.5 Follow-Up Procedures for OS Participants

OS participants will be followed up by annual newsletters, an annual mail contact to collect Medical History Updates, and a third-year CC visit (at which time the baseline clinical measurements will be repeated).

8.5.1 Annual Newsletter

All OS participants receive a trial-wide WHI newsletter (*WHI Matters*) once a year during the sixth month after their enrollment month. The goal of the newsletter is to present news about WHI, promote retention, and to keep up-to-date addresses for participants. For a detailed description of the newsletter and procedures for updating addresses for undeliverable newsletters, refer to *Section 17.1.5 - Participant Newsletter*.

8.5.2 Annual Mail Contact

Follow-up data (Medical History Update and exposure information) are collected annually from OS participants during the nine years following enrollment. Activities to collect the data consist of a series of mail and telephone contacts during the follow-up period. Data collection attempts by mail are conducted by the Clinical Coordinating Center (CCC) on an annual basis, except during the participant year 3 when data are collected by the CC during the follow-up clinic visit. For a full discussion of procedures, refer to *Section 16.5 - OS Annual Mail Contact and Follow-Up of Non-Responders.*

8.5.3 Follow-Up of Non-Respondents

For participants who do not respond to the CCC's annual mailed contacts, data collection attempts by telephone are conducted by the CCs on an every other year basis. Refer to *Section 16.5.3 - CC Data Collection for Non-Respondents to OS Mailings.*

8.5.4 Three Year Visit to CC

Clinic Visits are conducted for OS participants in the third year following enrollment. Refer to *Section 16.3 - Annual (CT) and Third Year (OS) Visit* for a description of the procedures and activities for this visit.

Figure 8.1

Telephone Script for Enrolling OS Women by Mail
(For Those Who Have Completed OS Screening Tasks That Require a CC Visit)

"Hello Ms./Mrs. _____, this is _____ from the Women's Health Initiative (name of clinical center) ."

For women who became ineligible for the CT between screening visits:

"We have reviewed the forms and results of the tests you recently completed during your visit to our Clinical Center. Based on these results, we have found that you are eligible to join the health tracking or "Observational" part of the study."

If woman asks for reason for ineligibility, give her the reason if that is your clinic's policy. If not:

"There are many considerations that go into the decision as to whether or not you are eligible to join the study. We take all of the information we have collected on you - your physical measurements, health history, medication and hormone use, and dietary habits and enter it into the computer. The computer has a formula that considers all of this information and determines whether you are able to join the study."

For women who are not interested in joining the CT:

"We have reviewed the forms and results of the tests you recently completed during your visit to our Clinical Center. We understand that you are not interested in joining the Hormone or Dietary Studies, so we would like to invite you to join the health tracking or Observational Study instead."

For women who were screened months ago and were found to be ineligible for CT:

"We have reviewed the forms and results of the tests you completed some time ago during your visit to our Clinical Center. Your results indicated that you were not eligible to join the parts of the study going on at that time. Since that time, we have started the health tracking or "Observational" part of the study, and would like to invite you to join."

Continue for all women:

"The purpose of the Observational Study is to learn more about women's health in general and about the causes of disease in women. If you join the Observational Study, first we will send you questionnaires for you to complete at home. Then once a year for the next 8-12 years we will mail you health updates that consist of three short questionnaires. You will fill these questionnaires out in your home, and return them to the Clinical Center in the postage-paid return envelope provided."

For women not at bone density sites:

"In addition to filling out these questionnaires, you will need to come in for another clinic visit in three years. During this visit, you will have similar procedures and measurements as those done at the screening visit. There will be some physical measurements such as height and weight, and a blood sample will be drawn."

For women at bone density sites:

> "In addition to filling out these questionnaires, you will need to come into the clinic every three years for tests similar to the ones you have already done. This means that you will come into the clinic for three more visits: one in three years, one in six years, and one in nine years. This includes physical measurements such as height and weight, and a blood sample will be drawn. You will also have your bone density measured and will be asked to provide a urine sample."

Continue for all women:

"We plan to enroll a total of 100,000 women from all over the U.S. in this study. We want the results of this study to represent all women, so if you're interested, we'd really like you to join. Can we send you the questionnaires for the Observational Study?"

If no:

> "I'm sorry that you won't be able to join the study. I would like to thank you very much for your interest in the Women's Health Initiative and for the time you have already spent in the study. If you should change your mind, please give us a call at the Clinical Center and we'll see about enrolling you in the study. Thanks again for your time."

If yes (and screened after Sept. 1):

> "Great! In the next few days we'll be sending you a packet containing the materials you will need to become a member of the Observational Study. In the packet you will find several items, including consent forms, several health questionnaires, and a postage-paid envelope. When you receive this packet, you will need to sign the consent forms, fill out the health questionnaires, and mail everything back to us in the stamped envelope. There will be instructions included in your packet that explain this in greater detail."

If yes (and screened before Sept. 1):

> "Great! In the next few days we'll be sending you a packet containing the materials you will need to become a member of the Observational Study. In the packet you will find several items, including consent forms, new health questionnaires, a copy of some of the questionnaires you filled out already, and a postage-paid envelope. When you receive this packet, you will need to sign the consent forms, fill out the new health questionnaires, and review and update the old questionnaires. Then you will need to mail everything back to us in the stamped envelope. There will be instructions included in your packet that explain this in greater detail."

Continue for all women:

"Do you have any questions?"

Answer any questions, then wrap it up:

"In about six months we'll send you a copy of the WHI newsletter to help keep you informed about the progress of the study. This newsletter will arrive every year for the next 8-12 years. Also, in one year you will receive the health update questionnaires mentioned earlier, which you will complete and mail back to the clinic. In about three years we'll give you a call to let you know that it's time to come in for your three year visit."

"We appreciate your interest in the Women's Health Initiative. Please call us when you receive your packet if you have any questions about filling out your forms, or if you have any questions about the study in general. Thank you for your time."

Figure 8.2

Telephone Script for Follow-Up Reminder to OS Women
(For Those Who Have Not Returned Their Questionnaires by Three Weeks Post-Mailing)

The caller should telephone until she/he is able to reach the woman. If woman is unavailable, leave a message with a relative or on a machine for her to call the clinic.

"Hello Ms./Mrs. _____, this is _____ from the Women's Health Initiative (name of clinical center)."

If packet mailed:

"A few weeks ago a packet of questionnaires was given to you or mailed to you from the Women's Health Initiative. Did you receive the packet?"

If no:

"I'm sorry to hear that." (***if mailed:*** "Perhaps it was sent to the wrong address.") "Let me confirm your mailing address so that we can send you out another packet."

(Confirm address, thank participant, terminate call, mail new packet.)

If yes:

"Good! Have you had time to complete the questionnaires?"

If yes:

"Great! Thanks very much for your quick response. Could you please return the materials to us right away in the postage-paid envelope? This would include one copy of the consent form with your signature and the completed health questionnaires. We can't officially enroll you in the study until we have received all of your materials."

(Participant response)

"Thank you very much for your time and for your interest in joining the Observational Study. We're very glad to have you as part of the study."

If no:

"Do you have any questions about the forms that I could answer for you?"

If yes, answer questions, then continue:

If no, continue:

"Could you please fill out the forms as soon as possible and return them to us here at the Clinical Center? We can't officially enroll you in the study until we have received all of your forms."

(Participant response)

"Thank you very much for your time and interest in joining the Observational Study of the Women's Health Initiative. We're very glad to have you as part of the study."

If at any point she indicates that she does not want to join the Observational Study (enter as refusal):

"I'm sorry that you won't be able to join the study. I would like to thank you very much for your interest in the Women's Health Initiative and for the time you have already spent in the study. If you should change your mind in the next few weeks, please give us a call at the Clinical Center and we'll see about enrolling you in the study. Thanks again for your time."

Figure 8.3

Telephone Script for Contacting OS Women to Participate in OS-Measurement Precision Study

The following is a suggested script that can be used when contacting OS participants:

"Hello Ms./Mrs._____, this is _____ from the Women's Health Initiative [name of clinical center]. As you may remember when we explained the Observational Study to you, some women who enroll will be invited to return to the clinic to repeat some measurements from the original visit. This repeat visit is very important because it will help us test how accurate and reliable our WHI forms are in collecting research information. You are one of the women who has been selected at random by the computer to return to the clinic for this repeat visit."

"Your participation in this repeat visit is voluntary and you have the right to decline without affecting your participation in the Observational Study. If you do agree, we will mail you four of the questionnaires you completed before and ask you to complete them again at home. We will then schedule a return visit to the clinic. At that visit we will collect the forms you completed and you will have another fasting blood draw. That is all we would need; none of the other procedures or forms will be repeated. The clinic visit will take approximately _____ [amount of time relative to your clinic-specific procedures]."

"Do you have any questions? Are you willing to do this repeat visit?"

For women who specifically refuse to return to the CC for the repeated blood draw:

"If you don't want to return to the clinic for the blood draw, would you be willing to help us by just completing the four questionnaires and mailing them back to the clinic? [If yes, mail her the forms with a self-addressed, stamped envelope. Continue to "all" script. If no, continue to script for "women who are not interested in joining the Measurement Precision Study."]

For women who are NOT interested in joining any of the Measurement Precision Study:

"We do appreciate all you've done so far in the Observational Study. Remember, your decision doesn't affect your participation."

For women who are interested in joining the Measurement Precision Study:

"Great! Let's schedule an appointment for your repeat clinic visit. [Schedule a convenient appointment.] Your return visit to _____ is scheduled for _____ at _____ . I will mail you the forms to complete. You should receive them within the next week. It is important that you try to complete the forms before you come to the clinic for your appointment. We look forward to seeing you again."

ALL

"We are so glad you are a part of the Women's Health Initiative. Thank you very much for your time."

Figure 8.4

OS Measurement Precision Study Cover Letter

Dear Participant:

Thank you for being part of the Measurement Precision Study of the Women's Health Initiative! As a participant in the study you are being asked to repeat four of the forms you filled out during, or before, your recent visit to our clinical center. This study will provide scientific information on how well the forms used in the Women's Health Initiative are working.

(PARAGRAPH FOR CCs in GROUP A) Please complete the enclosed four forms, using the #2 pencil we have provided. *Form 2 - Eligibility Screen* is a version of the form you filled out before joining our study. To reduce the number of questions you have to answer, several questions on this form have been crossed out. You do not need to answer those questions. *Form 30 - Medical History Questionnaire* asks about your history of hospitalizations and medical conditions. *Form 37 - Thoughts and Feelings* asks about your social relationships, feelings and experiences. *Form 42 - Observational Study Questionnaire* asks about your habits and lifestyle.

(PARAGRAPH FOR CCs in GROUP B) Please complete the enclosed four forms, using the #2 pencil we have provided. *Form 20 - Personal Information* asks for information about your age, education, and occupation. To reduce the number of questions you have to answer, several questions on this form have been crossed out. You do not need to answer those questions. *Form 31 - Reproductive History Questionnaire* requests information about your pregnancies and reproductive health. *Form 32 - Family History Questionnaire* contains questions about members of your family and diseases that your relatives may have had. *Form 34 - Personal Habits Questionnaire* asks about your health habits, such as smoking and exercise.

(PARAGRAPH 1 AND 2 (FOLLOWING) FOR ALL WOMEN WHO DO ACCEPT THE BLOOD DRAW) Remember to bring your completed forms with you when you return to have your blood drawn. Your return visit to_____

is scheduled for _____ at _____.

This visit is to draw a fasting blood sample as part of our Measurement Precision Study. It is important that you take no aspirin or anti-inflammatory drugs (prescribed or over-the-counter for example, ibuprofen, Advil, or Motrin) for 48 hours before the clinic visit and have nothing but water to eat or drink during the 12 hours before the clinic visit. If you usually take medications other than aspirin or anti-inflammatory drugs in the morning, you may take them with water at the usual time. You should not take medicines for diabetes until after the blood draw, unless your doctor has given you other instructions. During the 12 hours before your clinic visit, you should also not do any vigorous exercise. In addition, you should not smoke for one hour before your blood draw.

(ALTERNATE PARAGRAPH FOR WOMEN WHO DO NOT ACCEPT TO DO THE BLOOD DRAW) Please mail the completed forms back to us in the enclosed return envelope. If you have any questions, please call us at _____.

As always, all information you provide will be kept confidential and your name will not be linked with data given to anyone other than the researchers in this study. Participation in this study is voluntary and you may refuse to answer any questions on the forms. However, it is very important to have complete information on all participants in our Measurement Precision Study to make sure that the results are accurate and scientific.

We appreciate your participation in this special part of the Women's Health Initiative. This is an important part of our efforts to improve the health of women for generations to come. Every woman counts, so please be sure to complete these questionnaires carefully and completely.

We look forward to seeing you again! If you need to change your appointment time or have any questions, please call us as soon as possible at _____.

Sincerely,

Section 8
Observational Study

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