SECTION 4

SCREENING

INTRODUCTION

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

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

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

4.1. Screening Visits for WHI

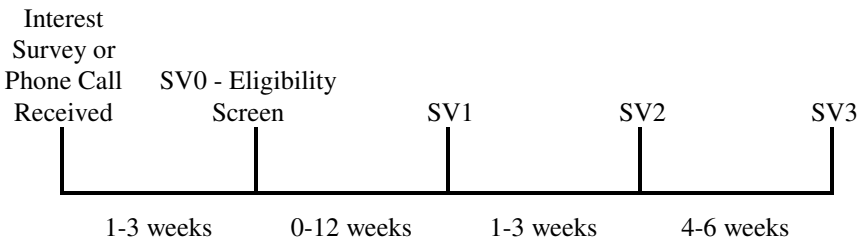
There are three screening visits for the WHI: Screening Visit 1 (SV1), Screening Visit 2 (SV2), and Screening Visit 3 (SV3). CCs complete one prescreening contact (Screening Visit 0 or SV0) via phone, mail, or a visit, at which the woman is asked to complete *Form 2/3 - Eligibility Screen* and other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

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

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

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

Figure 4.1
Recommended Time Between Screening Visits



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

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

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

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

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

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

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

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

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

Figure 4.3
Overview of SV1 (Recommended)

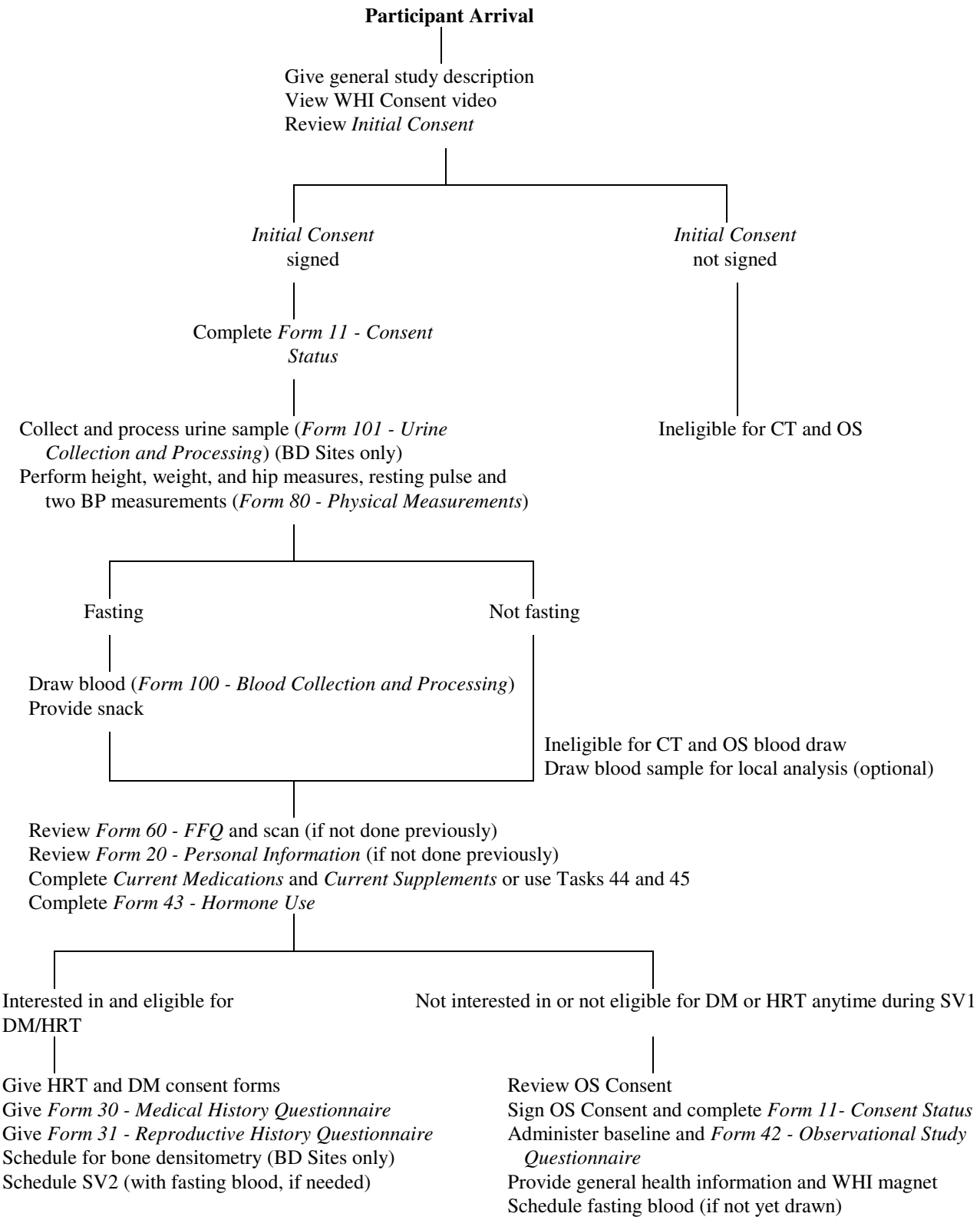


Figure 4.4
Estimated SV2 Activity Times

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

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

Figure 4.5
Overview of SV2 (Recommended)

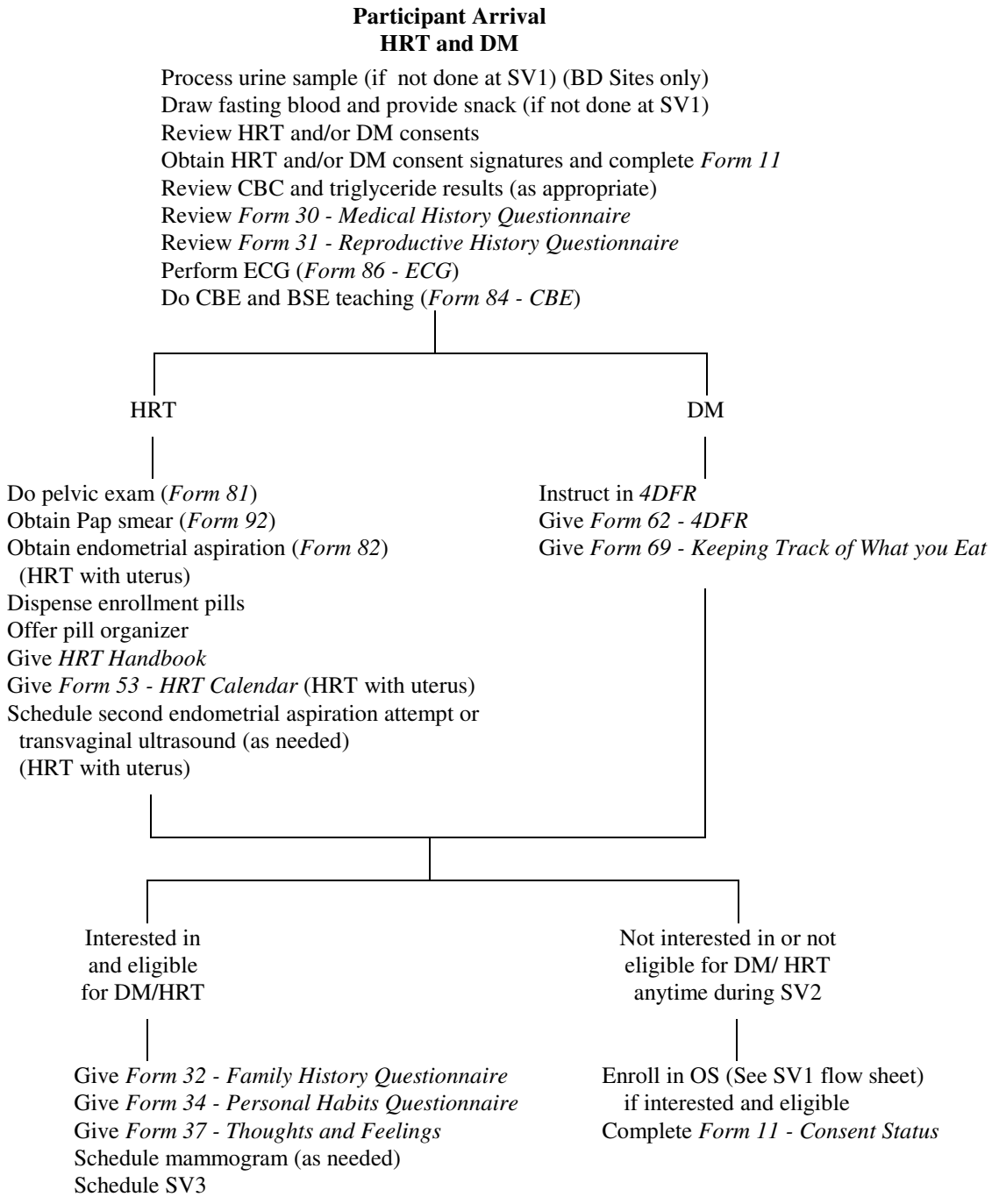
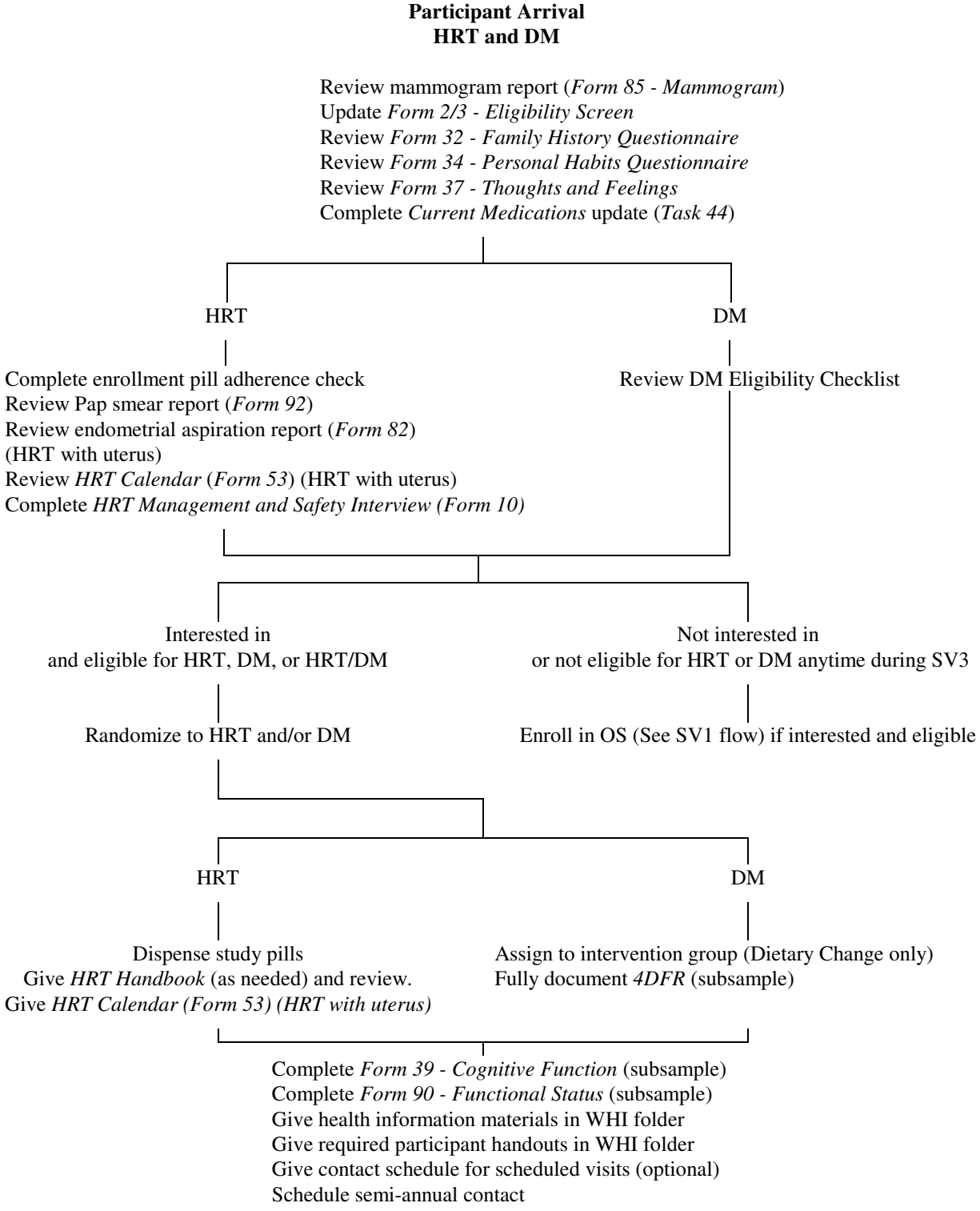


Figure 4.6
Estimated SV3 Activity Times

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

Figure 4.7
Overview of SV3 (Recommended)



4.2. SV1

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

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

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

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

4.2.1. Purpose of SV1

The purpose of SV1 is to:

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

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

The SV1 is challenging to the CC because:

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

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

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

4.2.2. Activities During SV1 (Recommended)

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

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

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

4.2.3. Preparation for SV1

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

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

4.2.3.1. Two Weeks Before SV1

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

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

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

4.2.3.2. One Day Before SV1

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

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

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

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

4.2.4. Guidelines for SV1 Activities

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

4.2.4.1. Reception

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

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

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

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

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

4.2.4.2. General Study Description (Required)

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

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

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

4.2.4.3. Initial (Screening) Informed Consent (Required)

a) Description of the WHI Study and Screening Visits

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

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

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

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

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

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

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

b) Requirements of the Initial Informed Consent Process

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

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

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

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

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

c) The *WHI Consent Video* (Required)

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

d) Reviewing the Initial Consent Form (Required)

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

e) Signing the Initial Consent Form (Required)

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

f) Signing the General Medical Release Form

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

4.2.4.4. Blood Draw (Required)

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

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

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

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

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

4.2.4.5. Questionnaire Review (Required)

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

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

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

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

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

c) **Eligibility Items**

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

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

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

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

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

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

a) Current Medications

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

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

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

b) Current Supplements

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

Eligibility Items:

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

Oral Corticosteroids

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

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

4.2.4.7. Physical Measurements (Required)

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

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

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

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

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

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

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

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

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

b) Waist and Hip Circumference

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

c) Resting Pulse

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

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

d) Blood Pressure

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

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

Systolic blood pressure > 200 mm Hg

Diastolic blood pressure > 105 mm Hg

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

4.2.4.8. Urine Collection (Bone Densitometry Sites)

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

4.2.4.9. CT Informed Consent (Required)

a) Description of CTs

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

General CT

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

HRT Intervention (HRT)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Dietary Modification Trial (DM)

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

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

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

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

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

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

Dietary Change Group

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

Comparison Group

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

b) Review of CT Consent Forms

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

c) Signing of CT Consent Forms

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

4.2.4.10. Hormone Interview (Required)

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

4.2.4.11. Distribute Forms to CT Participants (Recommended)

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

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

4.2.5. Observational Study Participants

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

4.2.5.1. OS Informed Consent (Required)

a) Description of the OS

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

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

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

b) Review of OS Consent Form (Required)

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

c) Signing the OS Consent Form (Required)

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

4.2.5.2. Distribute Questionnaires to Observational Study Participant (Required)

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

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

4.2.5.3. Completing SV1 for OS Participants (Required)

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

4.2.5.4. OS Enrollment (Required)

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

4.2.6. Exit Interview

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

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

Inform the participant of what to expect during SV2.

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

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

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

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

4.2.6.1. Schedule an Appointment for SV2

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

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

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

4.2.6.2. Participant Hand-Outs (Required)

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

- Copy of *Initial Consent* (Required)

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

4.2.7. Post-Visit Review

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

4.2.7.1. Blood Analysis Results (Required)

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

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

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

To review blood results:

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

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

4.2.7.2. Scanning and Key-Entry of Data from SV1

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

4.3. SV2

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

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

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

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

4.3.1. Purpose of SV2

The purpose of SV2 is to:

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

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

4.3.2. Activities During SV2

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

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

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

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

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

4.3.3. Preparation for SV2

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

4.3.3.1. Two Weeks Before SV2

Two weeks before SV2:

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

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

4.3.3.2. One Week Before SV2

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

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

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

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

4.3.3.3. Activities on the Morning of SV2

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

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

4.3.4. Guidelines for SV2 Activities

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

4.3.4.1. Reception

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

4.3.4.2. Clinical Trials Consent Form (Required)

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

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

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

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

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

4.3.4.3. Review of Questionnaires (Required)

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

4.3.4.4. SV2 Procedures

a) ECG (Required)

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

b) Review Complete Blood Count (Required)

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

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

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

c) Clinical Breast Exam (CBE) (Required)

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

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

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

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

e) Mammogram (Required)

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

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

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

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

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

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

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

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

g) Endometrial Aspiration (HRT) (Required)

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

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

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

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

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

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

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

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

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

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

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

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

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

k) 4DFR Instruction (Required)

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

4.3.4.5. Observational Study Participants

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

4.3.5. Exit Interview

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

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

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

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

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

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

4.3.5.1. Schedule an Appointment for the Third Screening Visit

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

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

4.3.5.2. Participant Hand-Outs

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

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

4.3.6. Post-Visit Review

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

4.3.6.1. Blood Analysis Results (Required)

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

4.3.6.2. Mammogram Results (Required)

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

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

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

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

4.3.6.3. Pap Smear Results (HRT) (Required)

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

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

4.3.6.4. Endometrial Aspiration (HRT) (Required)

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

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

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

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

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

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

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

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

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

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

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

4.3.6.7. Participants Whose Test Results Indicate Ineligibility (Required)

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

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

4.4. SV3

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

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

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

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

4.4.1. Purpose of SV3

The purpose of SV3 is to:

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

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

4.4.2. Activities During SV3

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

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

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

4.4.3. Preparation for SV3 (Required)

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

4.4.3.1. Two Weeks Before SV3

Two weeks before SV3, mail to the participant:

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

4.4.3.2. One Week Before SV3

One week before SV3:

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

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

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

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

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

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

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

4.4.4. Guidelines for SV3 Activities

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

4.4.4.1. Reception

See *Section 4.2.4.1 - Reception* for guidelines.

4.4.4.2. Assess HRT Enrollment Pill Adherence (HRT)

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

4.4.4.3. Review *Form 53 - HRT Calendar*

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

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

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

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

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

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

4.4.5. Pre-Randomization Discussion

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

4.4.5.1. HRT Eligibility Discussion

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

4.4.5.2. DM Eligibility Checklist

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

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

4.4.5.3. Questionnaire Review

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

4.4.5.4. Current Medications Update

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

4.4.5.5. Functional Status Measures (Subsample)

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

4.4.5.6. Cognitive Assessment (HRT; Subsample)

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

4.4.6. Randomize Participant (Required)

Key-enter or scan forms completed at SV3.

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

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

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

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

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

4.4.8. Exit Interview

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

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

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

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

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

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

4.4.8.1. Participants Assigned to the DM Dietary Change Group

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

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

4.4.8.2. Participants Assigned to the DM Comparison Group

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

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

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

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

4.4.9. DM Participants Identified in 4DFR Subsample

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

4.4.10. Baseline Welcome Packet

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

Baseline Welcome Packet

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

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

4.4.10.1. Health Care Provider Packet (Optional)

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

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

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

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

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

4.4.12. Participant Materials (Required)

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

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

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

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

4.5. Eligibility

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

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

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

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

4.5.1. Determining Eligibility

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

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

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

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

4.5.2. Definition of Postmenopausal Status

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

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

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

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

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

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

4.5.2.1. HRT Menopause Algorithms (Figure 4.8)

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

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

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

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

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

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

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

4.5.2.2. DM and OS Menopausal Algorithms (Figure 4.9)

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

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

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

Figure 4.8
HRT Menopause Algorithm

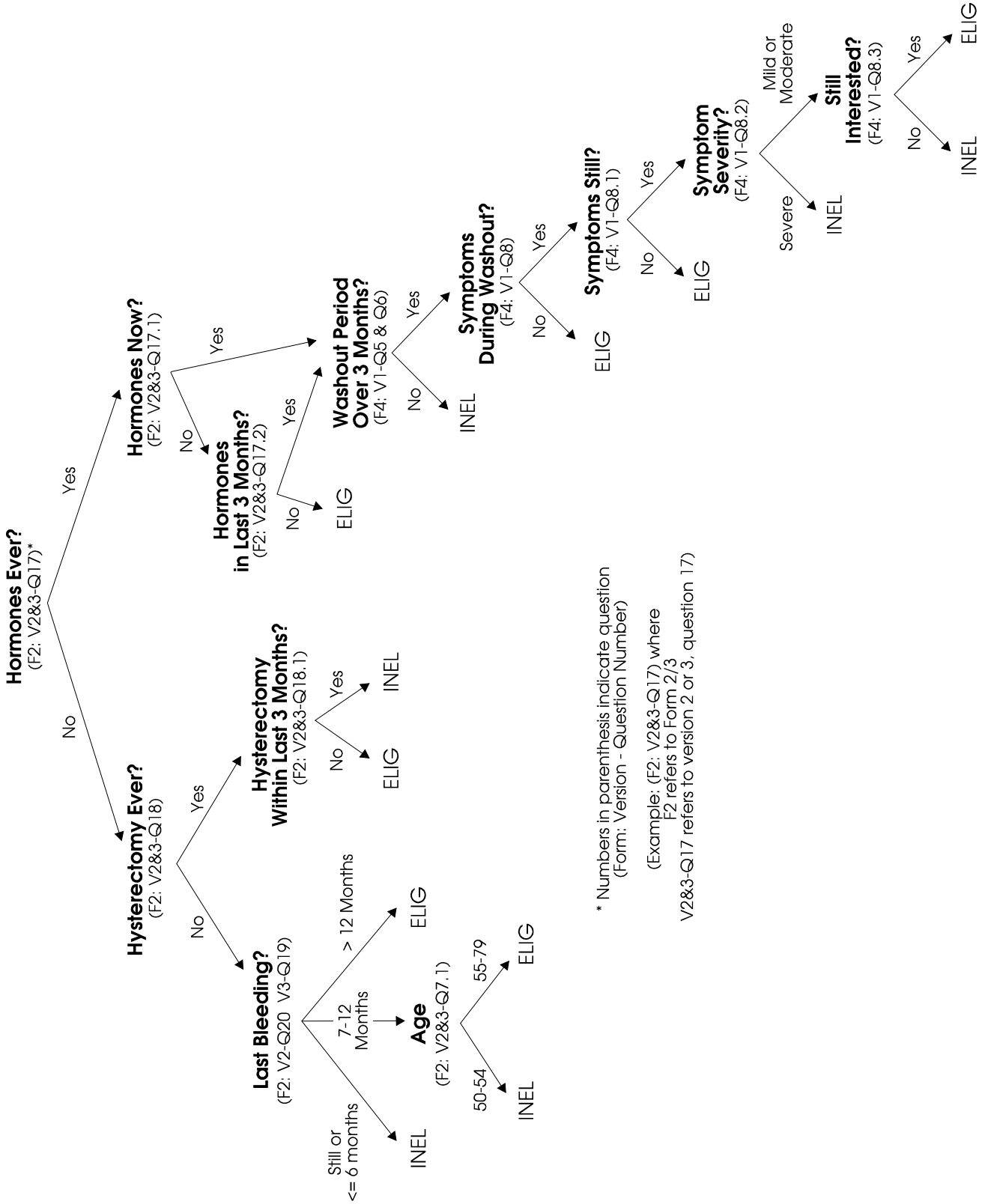
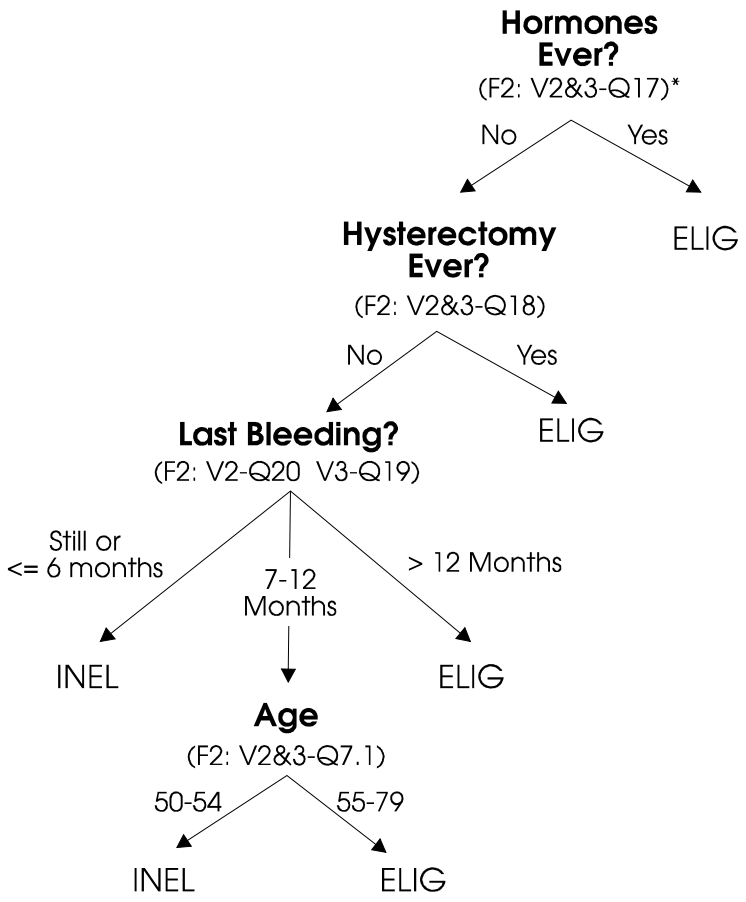


Figure 4.9
DM & OS Menopause Algorithm



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

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

4.5.3. Time Limits During Screening

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

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

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

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

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

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

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

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

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

4.5.4. Rescreening Ineligible Participants

4.5.4.1. Tasks to be Repeated Post-HRT Washout

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

measurements truly reflect intervention changes (e.g., hormones may affect cholesterol and triglyceride levels as well as some physical measures). You do not need to readminister any of the self-administered forms listed below that she may have completed before the HRT washout. For example, a woman may complete an SV1 and several self-administered forms such as *Form 30 - Medical History*. She may then decide she wants to go on an HRT washout to be eligible for HRT. You need to repeat the screening data collection you completed at the SV1, such as *Form 80 - Physical Measurements*, but you do not need to readminister the *Form 30 - Medical History*.

After the HRT washout, collect all baseline and screening data, except the self-administered forms listed below:

- *Form 2/3 - Eligibility Screen*
- *Form 20 - Personal Information*
- *Form 30 - Medical History Questionnaire*
- *Form 31 - Reproductive History Questionnaire*
- *Form 32 - Family History Questionnaire*
- *Form 34 - Personal Habits Questionnaire*
- *Form 37 - Thoughts and Feelings*
- *Form 60 - FFQ*

All baseline and screening data, excluding the self-administered forms listed above, must be collected after the participant completes her HRT washout, regardless of whether or not the encounter date for the original data is within the six months before randomization. If the encounter date for the original data is more than six months before randomization, you must recollect all the data as described in Part A above.

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

4.5.4.2. Ineligible on *Form 2/3 - Eligibility Screen*

If the woman is ineligible based on responses to questions on *Form 2/3 - Eligibility Screen*, stop the screening process. Do not conduct an SV0/SV1.

If the woman later becomes eligible, start the screening process again by completing a second *Form 2/3*. If the woman is now eligible by her responses to the second *Form 2/3*, schedule an SV1 and continue the screening process.

This *Form 2/3* rescreening procedure can only be completed for the criteria listed below. Use CC discretion and appropriate "future tickler" files to determine the time to rescreen for the criteria listed below.

Criteria on *Form 2/3* that can be rescreened:

- Age 47-49.
- Not likely to reside in area for three or more years.
- Active participant in another intervention trial.
- Colorectal cancer in the last 10 years (HRT only).
- Endometrial cancer in the last 10 years (DM only).
- Melanoma in the last 10 years (DM only).

- Other cancers in the last 10 years (except breast).
- Hysterectomy in the last three months.
- Pre-menopausal.
- Ten or more meals prepared away from home.
- Special diet for celiac sprue and other malabsorption syndromes.
- Low fiber, low-residue diet.
- DVT in the past six months.
- PE in past six months.
- Stroke in the past six months.
- TIA in the past six months.
- MI in the past six months.
- Medical condition associated with less than three years' predicted survival (e.g., lung disease, liver disease, heart failure).
- Lost 15 or more pounds in last six months.
- Can't come to the CC.

4.5.4.3. FFQ Rescreening

Women interested in the DM may complete a second screening FFQ (*Form 60*) one month after completing the initial FFQ if their initial screening FFQ (Form 60) is ≥ 29% and < 32% energy from fat (and their total energy intake is ≥ 600 kcal and < 5000 kcal.) A third FFQ is not allowed. The FFQ eligibility for women completing a second FFQ will use the same eligibility cutpoint (32%) as the initial FFQ.

This FFQ rescreening procedure is optional, at CC discretion. CCs are encouraged to consider the following when deciding whether or not to offer FFQ rescreening to a woman: (a) whether the CC needs this source of women to boost their DM recruitment, (b) clinic screening visit flow, (c) the 6-month screening visit window, and (d) staff resources. Clinics can decide whether or not to rescreen women on an individual basis when the FFQ eligibility report is run.

Note that this change to the FFQ rescreening procedure changes the minimum waiting time for rescreening on the FFQ from 12 months to one month, but limits the FFQ rescreening to women whose initial screening FFQ shows ≥ 29% and < 32% energy from fat (and total energy intake ≥ 600 kcal and < 5000 kcal.) To reduce the learning effect from repeating a task, CCs may choose to ask a woman to complete a second FFQ at a later time. This choice needs to be balanced with the 6-month screening window and the possibility of needing to recollect data.

We recommend that the Lead Dietary Assessment Nutritionist work with CC staff to train and implement these new procedures. Include training for all staff who work with the FFQ throughout the screening process.

4.5.4.3.1. Discussing the repeat FFQ option with screenees

CCs are encouraged to discuss the potential of completing a second FFQ with DM-interested women early in the screening process, ideally before they complete the initial FFQ.

Suggested script to use whenever the FFQ is first mentioned to a woman, e.g., during an in-person SV0 or to include with the cover memo you mail with *Form 2/3*, *Form 60* and *Form 61*:

"We occasionally ask women to fill out a second FFQ. This is a normal part of research. If we need you to fill out a second FFQ, it would usually be several weeks after you completed the first FFQ."

The reports that print out after each FFQ is scanned will not change. These FFQ scan reports will continue to print one of the following three messages:

- Eligible
- Ineligible: For calories
- Ineligible: For percent calories from fat

To determine which women are eligible to complete a second FFQ, you will need to run a DM eligibility determination in WHILMA for FFQ-ineligible women. You then run the *DM Eligibility Determination* report (*WHIP 0181)* for these women and the new CC report, *Members Eligible for FFQ Rescreening (WHIP 0741).* After running these reports, Clinical Centers may decide whether or not to offer the FFQ rescreening option to a woman.

- DM Eligibility Determination Report.

The informational comment for "FFQ Pct Calories from Fat/Energy Intake" criterion on the *DM Eligibility Determination* report (*WHIP 0181*) has been modified to read "May be eligible for rescreening" for women whose percent calories from fat is < 32% and ≥29% and whose total energy intake is ≥600 kcal and <5000 kcal.

- The Members Eligible for FFQ Rescreening Report:

The *Members Eligible for FFQ Rescreening* report (*WHIP 0741*) lists all DM screening participants:

- Whose FFQ was scanned thirty or more days ago.
- Who have a daily percent calories from fat per FFQ ≥ 29% and < 32%.
- Who have not already completed a second FFQ.
- Who are not ineligible for DM for any other reason.

Suggested script when asking a woman to complete a second FFQ:

"We need more dietary information from you before we can continue your screening for the dietary part of the WHI. We will get this information by having you complete a second FFQ one month [or the time frame selected by the CC] from now. Our staff will schedule an appointment for you now.

Suggested script for telling women they are ineligible for DM:

"Based on DM eligibility criteria, you are not eligible for the dietary part of the WHI. We'd like to talk with you about being an important part of the Hormone Replacement Therapy study or the Observational study."

Clinics may choose to recontact women whose FFQs were scanned before March 15, 1996 and who were ineligible for the DM per FFQ, and who are not enrolled in the OS.

Suggested script for asking women to return to complete an FFQ after they have already been told that they are not eligible for the DM based on their first FFQ, i.e., women whose FFQs were scanned before March 15, 1996 and who are not enrolled in the OS:

"Some time ago you were contacted about participating in the Women's Health Initiative. We appreciated your interest in this important study and were disappointed when you were ineligible for the Dietary Modification study. There is a chance that you may be eligible now. We would like to offer you the opportunity to complete the enclosed FFQ and return it to the Clinical Center. We want to make sure that as many women as possible have the chance to participate in the Women's Health Initiative. Thank you very much for your help!"

4.5.4.4. Ineligible at SV1 or Later Screening Visits

If a woman is ineligible for the CT and OS based on data collected at any point during screening, stop the screening process at that point and do not conduct further screening visits. If the woman becomes eligible later based on that criterion, repeat data collection for the previously-excluding criterion and continue the screening process from the point at which you stopped. Repeat data collection for any data that exceed the time limits given in *Section 4.5.3 - Time Limits During Screening* above. Refer to *Section 4.5.4.3 - FFQ Rescreening* for specific details on FFQ rescreening criteria..

If the woman is ineligible for the CT based on criteria that can be re-evaluated (see list below), you can give her the option of joining the OS or waiting to see if she can become eligible for the CT at a later date. If you enroll a woman in the OS you cannot rescreen her for the CT. Keep in mind that women you rescreen may be poor compliers.

This rescreening procedure can only be completed for the criteria listed below. See the list for time restrictions on specific criteria. Use CC discretion and appropriate "future tickler" files to determine the time to rescreen for the criteria listed below.

Criteria at SV1 and Later

- Depression (*Form 6 - Final Eligibility Assessment*)
- Drug use (*Form 6 - Final Eligibility Assessment*)
- Alcohol use (*Form 6 - Final Eligibility Assessment*)
- Staff impression (*Form 6 - Final Eligibility Assessment*)
- No HRT or DM Consent (*Form 11 - Consent Status*)
- Current use of anticoagulants (*Task 44*) (Wait one week after stopping the anticoagulant before drawing blood.)
- *FFQ* - % calories from fat ≥ 29% and < 32% and total energy intake ≥600 Kcal and <5000 Kcal. (*Form 60 - FFQ*) (Refer to *Section 4.5.4.3 - FFQ Rescreening*)
- SBP > 200 or DBP > 105 (*Form 80 - Physical Measurements*)
- BMI < 18 (*Form 80 - Physical Measurements*)
- Suspicious CBE (*Form 84 - Clinical Breast Exam*) or Mammogram (*Form 85 - Mammogram*).
- Pelvic exam (*Form 81 - Pelvic Exam)*, Pap smear (*Form 92 - Pap Smear*), endometrial aspiration (*Form 82 - Endometrial Aspiration*), and transvaginal ultrasound (*Form 83 - Transvaginal Uterine Ultrasound*).
- HCT < 32% (*Form 100 - Blood Collection and Processing*)
- Platelet count < 75,000 cells/ml (*Form 100 - Blood Collection and Processing*)
- HRT enrollment adherence < 80% or > 120% (*Task 951*) (Can repeat enrollment adherence once if there is a good reason to believe the participant will not have further adherence problems after she is randomized.)

4.5.5. Waiver of an Eligibility Criterion

To try to minimize CC staff burden in evaluating eligibility, most criteria are assessed through closed-ended questions that are checked in the database. The questions themselves were designed to screen women as efficiently as possible while being true to the protocol definition. In some instances the eligibility criteria as determined by these questions are somewhat less flexible than the protocol. A waiver mechanism implemented by the CCC is available to address this discrepancy.

The Inclusion/Exclusion criteria from the protocol and other protocol restrictions on randomizations are listed below. Also listed is whether or not a waiver for the criteria will be considered. Some criteria are based on CC evaluation entirely (denoted by "CC") and thus no CCC intervention is needed. For temporary exclusions (denoted by "*"), CCs should follow the usual process for rescreening women rather than requesting waivers. (See *Section 4.5.4 - Rescreening Ineligible Participants* above.) If the rescreening does not resolve the situation, waivers will be considered only on those items indicated below. Waivers of safety criteria must be accompanied by adequate documentation of the reason the safety criterion is not a concern, such as correspondence with personal physician. (See examples given below in italics.)

Inclusion Criteria for All Components	**Waiver of Eligibility Criterion**		
	No Waiver Required - CC Staff Discretion	**CCC Will Consider Waiver**	
		NO	YES
*1. Postmenopausal female volunteers of all races and ethnicity, with or without a uterus or ovaries.		*x*	
*2. Ages 50-79 years, inclusive, at first screening contact.		*x*	
*3. Likely to be residing in study area for at least three years after randomization or enrollment.		*x*	
4. Providing written informed consent.		*x*	
A. Exclusion Criteria for All Components			
1. Competing Risk			
a. Any medical condition associated with predicted survival of less than three years in the judgment of a Clinic physician (e.g., class IV congestive heart failure, obstructive lung disease requiring long-term ventilation or supplemental oxygen in the past, sever chronic liver disease with jaundice or ascites, kidney failure requiring dialysis, sickle cell anemia).	*x*		
2. Adherence or Retention Reasons			
*a. Alcoholism	*x*		
*b. Other drug dependency	*x*		

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

Inclusion Criteria for All Components	Waiver of Eligibility Criterion		
	No Waiver Required - CC Staff Discretion	CCC Will Consider Waiver	
		NO	YES
*c. Mental illness, including severe depression	*x*		
d. Dementia	*x*		
*e. Active participant in any other intervention trial where participants are individually randomized to an intervention or control group. *Example: Woman responds that she is in a consumer products study and is randomly allocated to a given product with minimal additional time burden.*			*x*
B. Additional Exclusion Criteria for All CT Components			
1. Competing Risk			
a. Invasive cancer of any typein the past 10 years		*x*	
b. Breast cancer at any time (in situ or invasive)		*x*	
*c. Baseline mammogram or clinical breast examination findings questionable or suspicious of breast cancer		*x*	
*d. Acute myocardial infarction in past six months		*x*	
*e. Stroke or transient ischemic attack (TIA) in the past six months		*x*	
f. Known chronic active hepatitis or severe cirrhosis		*x*	
2. Safety Reasons			
a. Severely underweight (recommended limit of BMI < 18 kg/m^2 or unintentional loss of 15 or more pounds in previous six months)	*x*		
*b. Hematocrit < 32% *Example: Woman with thalassemia minor has low hematocrit. Since this is not an iron-deficient anemia, there are no safety concerns for DM. Document diagnosis of thalassemia minor and agreement of woman's provider to support participation.*		*x* (HRT)	*x* (DM)
*c. Platelets < 75,000 cells/ml		*x* (HRT)	*x* (DM)

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

Inclusion Criteria for All Components	Waiver of Eligibility Criterion		
	No Waiver Required - CC Staff Discretion	CCC Will Consider Waiver	
		NO	YES
Example: Woman has long-standing idiopathic thrombocytopeniawhich is stable in nature. No related conditions contraindicate participation in DM. Document nature of condition and agreement of woman's health care provider to support participation.			
*d. Severe hypertension (systolic BP > 200 mmHg or diastolic BP > 105 mmHg)		*x*	
e. Current use of oral daily corticosteroids		*x*	
3. Adherence or Retention Reasons			
a. Unwilling to participate in baseline or follow-up examination components such as mammograms, clinical breast exams, phlebotomy, electrocardiograms, questionnaires and form; or unable to complete baseline study requirements	*x*		
C. Additional Exclusion Criteria for Hormone Replacement Component			
1. Safety Reasons			
a. Endometrial cancerof any stage at any time		*x*	
b. Endometrial hyperplasiaat baseline biopsy or endometrial thickness > 5mm via ultrasonography (no rescreening)		*x*	
c. Malignant melanomaof any stage at any time		*x*	
d. History of non-traumatic pulmonary embolism or deep vein thrombosis, or deep vein thrombosis or pulmonary embolism ever	*x*		
e. Previous osteoporosis-related fracture being treated with HRT		*x*	
f. History of bleeding disorder serious enough to require transfusion		*x*	
g. Known history of hypertriglyceridemia, or lipemic serum leading to diagnosis of hypertriglyceridemia on baseline blood draw *Example: Woman with a recent bout of systemic infection (sepsis). Infection has resolved but triglyceride levels are still elevated (but resolving.) Document history and agreement of woman's health care provider to support participation.*			*x*
*h. Currently on anticoagulants		*x*	

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

Inclusion Criteria for All Components	Waiver of Eligibility Criterion		
	No Waiver Required - CC Staff Discretion	CCC Will Consider Waiver	
		NO	YES
i. Currently on tamoxifen		*x*	
*j. Abnormalities in baseline Pap smear, pelvic exam, or pelvic ultrasound (if performed)		*x*	
2. Adherence or Retention Reasons			
a. Severe menopausal symptoms that would make placebo therapy intolerable to the participant	*x*		
*b. Inadequate adherence with placebo enrollment (run-in) (less than 80% of daily pills taken) (only one repeat enrollment period is allowed)		*x*	
*c. Unable or unwilling to discontinue use of HRT (women must discontinue current replacement hormone therapy for at least three months before baseline measures for HRT enrollment)		*x*	
*d. Unable or unwilling to discontinue use of oral or injectable testosterone (must discontinue current testosterone use for at least three months before baseline measures for HRT enrollment)		*x*	
*e. Unwilling to have baseline or scheduled endometrial aspirations		*x*	
D. Additional Exclusion Criteria for Dietary Modification Component			
1. Adherence or Retention Reasons			
*a. Special dietary requirements incompatible with the intervention diet (such as celiac sprue, other malabsorption syndromes). Women will be eligible if they are on a diabetic dietor a low salt diet *Example: Woman has been prescribed a low fiber diet during acute episodes of malabsorption which happen infrequently (2-3 times per year) and last for less than a week. Except for these rare occurrences, the woman's normal diet would not exclude her from either the Dietary Change or Comparison Arms, justifying the waiver. Provide the CCC with documentation of the nature of woman's condition and the agreement of her health care provider in support of her participation.*			*x*
b. Colorectal cancerat any time		*x*	
c. Unable to complete Four-Day Food Record adequately	*x*		

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

Inclusion Criteria for All Components	Waiver of Eligibility Criterion		
	No Waiver Required - CC Staff Discretion	**CCC Will Consider Waiver**	
		NO	YES
*d. FFQ percent of calories from fat below a cut point chosen to exclude about 40% of screened women (may repeat assessment after one month if percent calories from fat is between 29-32 on first FFQ). FFQ energy intakes of < 600 kcal or >5,000 kcal at screening, regardless of percent energy from fat.		*x*	
*e. Number of main meals prepared out of home ≥ 10 per week	*x*		
f. Type I (insulin-requiring, ketosis-prone) diabetes mellitus			*x*
Example: Woman reports diagnosis of diabetes at age 12 and initiation of insulin therapy at age 15 causing routine exclusion as a type I diabetic. Medical records reveals this to be an early onset of type II diabetes found more commonly in Native American populations.			
g. Gastrointestinal conditions that contraindicate a high fiber diet	*x*		
h. Bilateral prophylactic mastectomy		*x*	
E. Additional Exclusion Criteria for CaD Component			
1. Competing Risk: The following "all components" and "all CT components" exclusion criteria will be reassessed just before randomization into the CaD component.			
a. Any medical condition associated with predicted survival of less than three years as described above (A.1.)	*x*		
2. Safety Reasons			
a. History of renal calculi		*x*	
b. History of hypercalcemia			*x*
c. Current use of oral corticosteroids		*x*	
d. Current use of calcitriol		*x*	
e. Unable or unwilling to discontinue use of vitamin D supplements more than 600 IU/day		*x*	
F. Other restrictions:			
1. Time limit on screening (6 months)		*x*(DM)	*x*(HRT)
2. Same day randomization for HRT and DM		*x*	
3. Completed baseline requirements (forms and procedures)			*x*

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

Inclusion Criteria for All Components	Waiver of Eligibility Criterion		
	No Waiver Required - CC Staff Discretion	CCC Will Consider Waiver	
		NO	YES
Example: Woman completes all aspects needed to determine eligibility above but refuses to provide some self-administered questionnaires after reminders and requests (e.g., Form 34 - Personal Habits Questionnaire or Form 37 - Thoughts and Feelings). CC determines the woman is an enthusiastic participant who wants to protect her privacy.			
4. Randomization within window of first annual visit for CaD			*x*
5. Limits on stratum enrollment (age, hysterectomy status)			*x*

* A woman who is temporarily excluded may be re-evaluated for eligibility as appropriate to the excluding condition. If more than six months have elapsed since the woman's SV1, however, most baseline and screening activities must be repeated.

** *Note:* HRT or HRT/DM participants may have their screening time extended to 9 months if a 6-month follow-up mammogram is needed to determine eligibility.

If you identify a woman who fails to meet an eligibility criterion as determined by the database but who satisfies the protocol definition of that criterion as determined by the CC PI or Clinic Manager, do the following:

1. Assess the woman's eligibility for that component on all other criteria selected to date. To do this, review the eligibility determination report for the woman and assure that all other criteria are evaluated as "ELIG."
2. Send an eMail to the CCC Data Coordinator requesting a waiver of eligibility criterion. In this request, specify the following information: WHI participant ID number for woman, study component(s) for which she is being considered, eligibility criterion in question, a brief statement explaining the rationale for the request for the waiver, and the date of the scheduled SV3. This information will be forwarded to the CCC Project Directors for review.
3. Allow at least 24 hours (one working day) for CCC evaluation and processing. The CCC Project Directors will evaluate each request for consistency with the intent of the protocol. If submitted in time and approved, a waiver of a particular criterion for that woman will be made in the database by the CCC in time for the SV3 but usually no sooner than one working day from receipt of request. You are strongly encouraged to submit a waiver request well in advance of the SV3 (2 weeks or more) to ensure that processing is complete before the scheduled SV3.

The CCC will keep a log of all requests for waivers and their final disposition. All waivers will be documented in the database for monitoring purposes.

4.5.6. Closure of Recruitment Cells

The CCC alerts a CC PI by memo when the CC has reached a cell-closing threshold for a specific recruitment cell ("stratum") and specifies a date for closing the cell. The thresholds are as follows:

Cells	Threshold (% of recruitment goal)
DM Age 50-54	85%
DM Age 55-59	100%
HRT Age 50-54	105%
HRT Age 55-59	105%

After the specific recruitment cell has been closed, you may not be able to randomize a participant to the closed recruitment cell. When you run an eligibility determination (Task 910 or 920) for a participant in a closed cell, WHILMA will return a result of INEL (ineligible) with the following two exceptions:

1. Women who began screening before the cell closure (that is, they have a *Form 2/3 - Eligibility Screen* with a contact date before the date of the cell closure) will not be found ineligible. You may continue these women in the screening process and randomize them as usual.
2. Women from minority groups are not excluded by a specific, closed recruitment cell at a CC. You will be able to randomize minority women to a closed recruitment cell, even if the *Form 2/3* contact date is later than the date the recruitment cell was closed.

In addition, women who are going into both DM and HRT may be randomized into both studies, even if their recruitment cell is closed in either HRT or DM (as long as a cell is still open in one of those studies.) In these circumstances, CCs must request a waiver of eligibility for the study that is affected by the cell closure before you can randomize the woman (see *Section 4.5.5 - Waiver of an Eligibility Criterion*).

4.6. Randomization and Enrollment

All women to be studied in WHI will be officially randomized into the appropriate CT components (HRT, DM, CaD) or enrolled into OS. All components have eligibility criteria that must be met before randomization or enrollment (see *Section 4.5 - Eligibility*).

The purpose of the randomization and enrollment procedure is to confirm eligibility, randomly assign a woman to an appropriate treatment arm, and maintain the double-blind nature of the study (for HRT and CaD).

4.6.1. Randomization into CT

Randomization is the time at which a woman becomes a participant in a CT; when she is officially randomized in the study and assigned to a treatment arm. Women need to be fully consented and screened for eligibility before the time of randomization. A woman will always be included in the CT for the purposes of analysis after she has been randomized ("intent to treat" analysis), so it is important to verify her willingness and eligibility before randomization. Although a woman may withdraw from active participation in the study (perhaps because she is no longer interested or because of some potential adverse effects), she will be included in her assigned arm in the primary analysis when comparing treatment arms.

Neither the woman nor the CC staff should be able to influence or predict a participant's treatment assignment. It is very important that the details of randomization be kept confidential. By randomly determining the treatment assignment, potential imbalances between treatment groups are minimized. One general feature that can be revealed, however, is that the randomization will be stratified by CC, age of woman (50-54, 55-59, 60-69 and 70-79), and by hysterectomy status for HRT. Thus, the randomization will keep a percentage of women of a given age group in each treatment arm of a trial (HRT, DM, or CaD) close to the randomization fraction for that arm. WHILMA will carry out the randomization.

For statistical analyses, the day of randomization represents the starting point for determining the effects of the intervention. Survival time and incidence rates for all of the endpoints will be calculated from the date of randomization. Since there are three CT components, each with their own randomizations, the analyses could become quite complicated if all the randomizations could occur at any time. To simplify the analyses and their interpretation, randomization to HRT and DM must occur on the same day; randomization into CaD will occur at the first annual visit (within a $\pm$ 4-week window of the target annual visit) or at AV2 if CaD was not offered to a participant at the AV1.

The process for all components will involve a specification of the components in which the woman is willing to participate, a confirmation of eligibility for each of these components, randomization to treatment arm(s) or enrollment into the OS, and a production of confirmation of randomization/enrollment report and member contact schedule.

4.6.2. Enrollment into OS

These women must meet minimal WHI eligibility criteria (see *Vol. 1 - Study Protocol and Procedures, Section 1 - Protocol, Section 4.4 - Study Population)* and sign the *OS Consent* indicating their willingness to be followed. The OS may be considered to be a single-arm study, with automatic assignment to that single-arm when enrolled in the OS.

4.6.3. Randomization and Enrollment Procedures (Required)

Detailed instructions for performing the randomization or enrollment for each component (HRT, DM, CaD, and OS) in WHILMA are given in *Vol. 5 - Data System, Section 6 - Eligibility Determination and Randomization*. Additional issues you must consider for each component are described below.

DM and HRT randomization for a DM+HRT participant must be done on the same day. Be sure to run an eligibility determination for each component to ensure she is eligible for both before you randomize her to one of the components. For example, if the woman is interested in both HRT and DM, run an eligibility determination in WHILMA for both components before you randomize into either. After randomization, you will not be able to enter or edit any baseline data for either component. If you are missing data for the second component, you will not be able to enter it nor randomize the women to that component.

4.6.3.1. HRT Randomization

The HRT randomization is blinded so neither the participant nor the WHI staff will know to which arm the participant is assigned. Dispense blinded study pills according to procedures in *Section 15.4.2 - Dispensing HRT Bottles at SV3.*

4.6.3.2. DM Randomization

The randomization process is not designed for participants to watch, and CCs should not allow DM participants to watch the randomization process in WHILMA. Explain to the participants that the selection of the Dietary Change vs. Comparison groups is done randomly and that CC staff have no influence over the selection of the group.

Participants are randomized to DM Dietary Change: Comparison Group in a 40:60 ratio. Therefore, CCs should see more participants randomized to the Comparison group than the Dietary Change group.

CCs can randomize women together in small groups under special circumstances, as listed below:

- Introducing group randomization: CC staff cannot initiate or propose group randomization to a participant without some indication that she is seeking this option. The participant must bring up the concept and indicate that her participation will be changed, limited, or ended if she is randomized to a different group from the other woman or women.
- Size of group: Women can be randomized in groups of two to eight women.
- Reasons for group randomization: Any one of the following three reasons is acceptable for deciding to randomize women in a small group:
    - The women share the purchasing, preparation, or consumption of their food;
    - The women live together.
    - The women have limited transportation and must carpool to and from the CC; or
    - Other situations may be considered (contact the CCC for review).
- The entire group must be randomized together. You must complete all eligibility requirements for all women in the group before a group randomization is performed. If any women in the group are also in HRT, they must be randomized to HRT on the same day. Notify the CCC Data Coordinator at least one working day before the group randomization will take place. Provide the CCC with the member IDs of the participants in the group and approximate time the women will be at your CC.

4.6.3.3. CaD Randomization

CaD Randomization may first occur at the first annual (or second annual visit for participants not offered CaD at AV1) visit. (see *Section 7.1.5 - Randomization Activities*.) The CaD randomization assignment is blinded so neither the participant nor the WHI staff will know to which arm the participant is assigned. Proceed with dispensing CaD study pills, according to procedures in *Section 15.4.5 - Selecting and Dispensing CaD Study Pills.*

4.6.3.4. OS Enrollment

Observational Study enrollment may occur at any step in the screening process after the participant is determined to be eligible. See *Section 8 - Observational Study* for more details.

4.6.3.5. Remote Site Randomizations

Clinical Centers have three issues to resolve before performing remote site randomizations:

- randomizations into HRT and/or DM
- identification of the DM Intervention subsample for documentation of the Four-Day Food Record (4DFR)
- dispensation of HRT study pills

Two Options for conducting the remote site randomizations are given below. Clinical Centers must use the procedures given below, and may use one or both of these depending on the needs of the remote site. The same guidelines for off-site randomizations will apply for annual visits and CaD dispensation when those activities begin at remote sites in the future. For more information about remote site visits, see *Section 2.1.3 - Remote Sites.*

Option 1: Randomization in WHILMA after bringing forms back to the main site

1. Prepare for the remote site visit:
   - Run the eligibility determination and appropriate reports to determine all activities that need to be completed at the Screening Visit 3 (SV3). For example, check to see if the participant is in the Functional Status or Cognitive Assessment subsamples.
   - For an HRT participant, determine how many bottles of enrollment pills she has and whether she is on her first or second run-in attempt. Take a box of HRT <u>enrollment</u> pills to the visit in case the participant will need additional enrollment bottles. Record the dispensing of any additional enrollment bottles on *Form 955 - Enrollment HRT Dispensing*.
2. Complete the usual SV3 activities and collect the information as usual from the participant. Complete *Form 44 - Current Medications (Backup)* if the participant is taking medications not captured at SV1.
   - DM participants must satisfactorily complete the DM Eligibility Checklist review process and have an acceptable 4DFR before they are eligible for DM.
3. Tell the participant that you will need to complete some of the activities of the visit at the Clinical Center and arrange a time to discuss results of these procedures and expectations by phone, as needed.
   - For HRT participants, follow-up activities include dispensing a bottle of the HRT study pills. Take the HRT enrollment bottle from the participant, and tell her you will be mailing her a new bottle the next working day. (This means the participant <u>must</u> be randomized within one working day.) Briefly review the pill instructions with the participant before she goes home, and remind her that all data will be reviewed to ensure her safety before the next bottle of study pills are mailed out to her. Verify her phone number and address, and tell her you will call her in one week to be sure she had received her next bottle of HRT pills.
   - For DM participants, follow-up activities include documentation of the 4DFR, if selected as part of the 4DFR subsample, and administration of the DM Post-Randomization interview. Verify the woman's phone number and tell her that the phone interview will take about 30-45 minutes. Schedule a time during the next week for the phone interview and let her know the name of the staff person who will contact her. Give her the information in writing.
3. Return to the CC and with all participant data and perform the key-entry of appropriate forms.

4. Run the final eligibility assessment and resolve any eligibility requirements. Complete the randomization in WHILMA within 1 working day of the remote site SV3.

   - For HRT participants, select the HRT study medication bottle and mail the bottle to the participant along with a copy of the medication instruction sheet or HRT Handbook.
   - For DM participants, determine if they are included in the 4DFR subsample. If included in the subsample, mail them a copy of their completed 4DFR before the scheduled follow-up phone call and ask them to have the copy of their completed 4DFR and a set of measuring cups and spoons to refer to during the phone call.

5. Complete a follow-up phone call with the participant.

   - For HRT participants, call the participant within 4-5 days of mailing the HRT study pills and ask the participant if she has received the bottle and if she has any questions about taking the pills. Review the pill instructions with her.
   - For DM participants, call the participant at the scheduled time to document the 4DFR, as needed, and conduct the post randomization interview. To streamline the time on the phone, review the 4DFR and identify the questions to ask her before the call.

Option 2: Randomization completed in WHILMA at the main site while conducting the SV3 at the remote site

1. Prepare for the remote site visit:

   - Try to collect all the baseline forms (e.g., *Form 30 - Medical History Questionnaire, Form 31 - Reproductive History Questionnaire, Form 32 - Family History Questionnaire, Form 34 - Personal Habits Questionnaire, Form 37 - Thoughts and Feelings, Form 38 - Daily Life*) from the participant before the SV3 and scan them into WHILMA before the SV3.
   - Schedule the SV3 with the staff at the main site so someone will be available to key-enter the forms faxed to the main site.
   - Run the eligibility determination and appropriate reports to determine all activities that need to be completed at the SV3. For example, check to see if the participant is in the Functional Status or Cognitive Assessment subsamples.
   - Set up a file to leave at the main site containing necessary information, such as participant barcode labels and enrollment bottle numbers dispensed (for HRT), needed for completing the randomization process.
   - Ensure the participant file you take to the SV3 has sufficient forms and preprinted participant barcode labels.
   - For an HRT participant, determine how many bottles of enrollment pills she has and whether she is on her first or second run-in attempt. Take a box of HRT enrollment pills to the visit in case the participant will need additional enrollment bottles.

2. Complete the usual SV3 activities and collect the information as usual from the participant. Complete *Form 44 - Current Medications (Backup)* if the participant is taking medications not captured at SV1.

   - For HRT participants, take the HRT enrollment bottle from the participant. Count the HRT enrollment pills, and use the conversion chart of enrollment pills to weights *Figure 4.16 - HRT Enrollment Pill Count to Pill Weight Conversion Chart* Record the HRT enrollment bottle number and pill weight on *Form 10 - HRT Safety and Management Interview, Question 5*. As usual, if additional enrollment pills are dispensed, randomization cannot occur at this visit. Record the dispensing of any additional enrollment bottles on *Form 955 - Enrollment HRT Dispensing*.
   - DM participants must satisfactorily complete the DM Eligibility Checklist review process and have an acceptable 4DFR before they are eligible for DM.

4. Phone the main site to verify that you are requesting randomization of the participant, giving the participant name and participant ID number. Fax copies of the forms needed for eligibility to the main site (see the sample list below). Put a participant ID label with barcode on each page of the forms that are faxed. Cover or remove the participant's name any other personal identifier from all forms before faxing the forms. For example, cover the participant's name on the first page of the form with a post-in note (so uncover after faxing) and blacken out the name on the other pages of the forms. Using the model SV3 in *Vol. 2, Section 4.4 - SV3*, you would fax the pages of the following completed forms to the main site:

    - *Form 2/3 - Eligibility Screen* updates, first page and any updated pages
    - *Form 6 - Final Eligibility Screen*, 2 pages
    - *Form 10 - HRT Management and Safety Interview* (HRT), first page
    - *Form 44 - Current Medications (Backup)*, all pages
    - *Form 53 - HRT Calendar* (HRT), first page
    - *Form 62 - 4DFR* (DM), last page
    - Baseline forms not collected previously, first page and other pages as needed

5. At the main site, key-enter the faxed forms as you would routine forms. For example, key-enter:

    - Edits to *Form 2/3 - Eligibility*
    - All of *Form 6 - Final Eligibility*
    - Hormone Replacement Therapy enrollment bottle number and weight for the appropriate enrollment bottle, as recorded on the first page of *Form 10 - HRT Management and Safety Interview* (HRT)
    - All of *Form 44 - Current Medications* (Backup)
    - Encounter information on *Form 10* (HRT), *Form 53* (HRT), and *Form 62* (DM)
    - Encounter information and other pages as needed on other forms
    - Note that you will need to key-enter rather than scan any required mark-sense forms. Initial the fax copy of each form as it is key-entered.

6. Run the eligibility determination and resolve any eligibility requirements with the staff at the remote site. Randomize the participant as usual.

    - For HRT participants, select the HRT study pill bottle and mail the bottle to the participant along with a copy of the medication instruction sheet or HRT Handbook.

7. Phone the remote site to verify that randomization for the participant is complete, giving the participant name and ID number. FAX the randomization information, including DM intervention assignment and selection of 4DFR subsample, and the participant contact schedule to the remote site; and file in the participant's file.

8. Complete activities of the SV3:

    - For an HRT participant, tell her you will be mailing her a new bottle of study pills within one working day. Briefly review the pill instructions with the participant before she goes home, but remind her that all data will be reviewed to ensure her safety before the next bottle of study pills are mailed out to her.
    - For a DM participant, conduct the post randomization interview. For DM participants selected for 4DFR subsample, complete the 4DFR documentation and conduct the post-randomization interview.

9. After the visit,

- Complete data entry of the forms.
- Complete the follow-up phone activities with an HRT participants by calling her within 3-4 days of mailing the HRT study pills and asking it she received the bottle and if she has any questions about taking the pills.

4.6.3.6. DM Group Randomizations

Randomizations of DM-eligible participants who wish to be randomized as a group will be done by the CCC on the next working day following the participants' SV3 (or following the earliest date that all participants in the group are ELIG for DM in WHILMA.)

Procedure

1. **Before SV3:**
   - Notify the CCC via email of a group randomization at least one working day in advance of the SV3. If your two-digit Clinical Center ID number is 11-45, contact Elena Mullin; if your clinic ID number is 46-68, contact Gretchen Van Lom. Provide the following information:
     - Date of SV3.
     - Participant ID numbers of participants to be randomized as a group.
     - Name and phone number of person to contact at the CC about the randomization.
2. You will receive acknowledgment of your email from the CCC. If you do not receive acknowledgment within 24 hours (excluding holidays and weekends), contact the CCC by telephone to confirm that the email was received.
3. **At SV3:**
   - Collect and enter into WHILMA all participant data (including any subsample tasks that need to be performed before randomization)
   - If any of the participants are to go into HRT as well as DM, conduct all of the usual HRT SV3 activities (Vol. 2, *Sec. 4.4.4 – Guidelines for SV3 Activities*) except for randomization and study pill dispensation.
   - Run eligibility in WHILMA for all studies that the participant is to be randomized into (DM and HRT). When you receive an ELIG result for all applicable studies, tell the participants that you will need to complete some of the activities of the visit the next day and arrange a time to phone the participant. See Vol. 2, *Section 4.6.3.5 - Remote Site Randomizations, Option 1, step 3* for items to discuss with the participants.
   - **Do not randomize the participants to DM or HRT at SV3 .**
4. **On the next business day FOLLOWING the SV3**:
   - Run DM eligibility (task 910 in WHILMA for all participants). It is necessary to do this so that an eligibility determination result of ELIG for the current date is in WHILMA when the CCC does the group randomization.
   - When you have obtained a result of ELIG for all participants in the group, notify your CCC contact **by 10:00 AM Pacific time** via phone or email that the participants are eligible and ready to be randomized to DM. (If notification is received later than 10:00 A.M., the group randomization may not be completed until the following day.)

Note: If one or more of the DM group participants are going into HRT as well as DM, it is the CC's responsibility to randomize the participant to HRT on the same day she is 'group-randomized' into DM by the CCC. It is recommended that you obtain an HRT status of ELIG before contacting the CCC to proceed with the DM group randomization, and that you wait until the CCC has confirmed completion of the DM randomization before you proceed with the HRT randomization.

5. Randomization of the DM group by the CCC

- After receiving CC confirmation of the ELIG results for participants in the group, the CCC will complete the group randomization by noon Pacific time on that day. The CCC will notify the contact person at the CC of the DM treatment arm (and 4DFR subsample, if applicable) via email that same day as soon as possible following completion of the randomization.

6. CC Follow-up

- Mail appropriate post-randomization materials:
  - Send appropriate Welcome Packet to all participants
  - Send HRT pills to HRT participants
  - Send a copy of the baseline 4DFR to DM participants selected for the documentation subsample
- Complete a follow-up phone call with the participants:
  - For HRT participants, call the participant within 4-5 days of mailing the HRT study pills and ask the participant if she has received the bottle and if she has any questions about taking the pills. Review the pill instructions with her. Confirm with the participant that she has started taking the study pills.
  - For DM participants, call the participant at the scheduled time to documents the 4DFR, as needed, and conduct the post – randomized interview. To streamline the time on the phone, review the 4DFR and identify the questions to ask her before the call.

4.6.4. Back-up Enrollment and Randomization

If WHILMA is not working when you need to enroll or randomize a participant, enrollment or randomization may be completed by contacting the Data Coordinator at the CCC who will enroll or randomize the participant centrally. Central randomizations will be supported only in the case of extended loss of computer functions. Otherwise, explain the problem to the participant and let her know you will contact her as soon as randomization can be completed and will mail her study pills and/or DM assignment status (depending on the CT component in which she is interested).

Figure 4.10
Nomogram for Body Mass Index

Figure 4.11
Initial Consent Script

Suggested Script for Initial Consent

"Now that you have watched the video and have a general idea of what the study is about, there are several more things I'd like to go over with you. I'm sure you have some questions about the study, and this may answer those questions.

First, I'd like to repeat some of what you've just seen in the video. The Women's Health Initiative is a study of women aged 50-79 and has four parts: hormone replacement, dietary change, an Observational Study, and a calcium and vitamin D study that will begin next year. The part you join will be decided by you and the CC staff, based on the results of your tests and on the information about yourself that you provide on your forms. The study is funded by the National Institutes of Health (NIH). A total of 164,500 women from all over the U.S. will be in the study.

Joining the study is completely voluntary and you may drop out at any time. You may choose to answer or not answer any question on the forms. Any information that you give is completely confidential and will only be seen by WHI staff, and, if necessary, the Food and Drug Administration (FDA), no one else. All of your answers are grouped with the answers of other women in the study, and only this grouped information is reported. Your name and other personal information will not be released in any reports or publications.

To decide which parts of the study you can join, you will go through some screening tests and activities. These will take place over three visits to the CC. At the first screening visit, there are several things that will be done.

Your height, weight, waist, and hips will be measured over non-blinding undergarments, and without shoes. You will also have pulse and blood pressure taken after you have been sitting for five minutes. You will be told what your blood pressure is, and whether you need to see your doctor for your blood pressure. There should be no risk involved in any of these procedures.

Next, about three tablespoons of blood will be drawn from a vein in your arm. Sometimes a woman may get a bruise or, very rarely, an infection may develop at the site of the blood draw. We will do everything possible to avoid these problems. There is no more risk for having your blood drawn here at the CC than there would be if your blood were drawn in your doctor's office.

On the basis of these tests, we will decide which parts of the study you can join, and then it's up to you to decide which parts you'd like to join. We may find that you are able to join either the hormone replacement or the dietary part, or you may be able to join both. If you are able to join both, it is up to you to decide whether you want to join one or both parts. We would like to encourage you to consider joining both. If you are not able to join either the dietary or hormone replacement therapy part, you may be able to join the observational study. After your screening tests, we will talk with you about which part(s) of the study you are eligible for and interested in joining.

Remember you may contact the CC if you have any questions at any time while you are in the study. What questions do you have at this time?"

Figure 4.12
HRT Consent Script

Suggested Script for Hormone Replacement Consent:

There are several points about the Hormone Replacement Trial that I would like to go over with you. I'm sure you have several questions about this part of the study, and this may answer some of those questions.

First, as with all parts of the Women's Health Initiative, taking part in the Hormone Replacement Trial is completely voluntary and you may drop out at any time. You may choose to answer or not to answer any questions on the study forms. Any information that you give is completely confidential and will only be seen by WHI staff and, if necessary, the Food and Drug Administration (FDA), and no one else. All of your answers are grouped with the answers of other women in the study, and only this grouped information is released. Neither your name nor any other type of identifying information will be released in any reports.

All women will be taking study pills. Some women will be taking study pills that don't contain any medicine. Others will either be taking study pills containing estrogen alone or study pills that have both estrogen and progestin, depending on whether or not you have a uterus. Neither of these two kinds of study pills has been proven to be more beneficial or safe than the other. A computer makes the selection for the groups so that it is fair. No one knows beforehand who will be taking active hormones or placebo. Before you sign up you must be willing to take part in either group. Both groups are equally important to the results of the study since everything we learn will come from comparing the groups. Once you begin, no one can take your place in the study group to which you have been assigned.

In order to take part in the hormone replacement trial, there are more tests that you will have. These include a mammogram, an electrocardiogram or EKG, and a physical examination. The physical examination involves a breast and pelvic exam, and if you have a womb, a Pap smear to check for cervical cancer. If you have a womb, you will also need to have a test of the lining of your womb (called an "endometrial aspiration"). There is a small risk of infection, bleeding and puncture of the uterus from the endometrial aspiration.

You can join if there are no health problems that might make taking part dangerous for you. You will be placed by computer into one of the groups and given your bottle of pills. Neither you nor the CC staff will know to which group you have been assigned. However, if there is some kind of medical emergency, we can quickly find out which group you're in and get this information to your doctor.

When you join, you will be asked to take a pill every day without fail. If you have a womb, you will be asked to keep track of any bleeding from your vagina, how heavy the bleeding is, and on what days it occurred. Of course, many women will not have any symptoms at all, which is also important to know. Four to six weeks after your last screening visit, a WHI staff person will call you to see how you are doing.

Regardless of which group you are placed in, you will be contacted by the CC every six months and you will have follow-up visits at the CC at least once a year to see how you are doing and to pick up study pills. Each of these visits will last about one hour. You will also have physical exams once a year for the nine to twelve years you are enrolled in the study and a breast exam, review mammogram results, and gynecologic exam (if you haven't had a hysterectomy), to make sure that everything is okay. At these visits, measurements and lab tests similar to the tests you have already taken will be done. These tests will include height, weight, and blood pressure. There is a small risk of bruise or slight infections, at the site of the blood draw; however the risk is no greater than if your blood were drawn in a doctor's office. You will be asked to have a mammogram annually. A mammogram uses radiation, which may slightly increase the risk of developing breast cancer. Scientists of the WHI and the National Cancer Institute believe that this small risk is outweighed by the benefit of finding breast cancer early. Mammograms every 1 to 2 years are recommended for all women in your age group. You will also have ECG every three years. You may also have measurements of your waist and hip,

physical abilities, or concentration and memory, blood draws, and/or endometrial aspirations, every three years.

There are several side effects that can occur as a result of taking study pills. These include headaches, bloating, changes in bowel movements, irritability, anxiety, depression, vaginal bleeding, breast tenderness, sleep changes, and nausea. While side effects are common among women taking hormones, some of the symptoms you may have could actually be related to changes that come with aging or menopause. Not all of you will have symptoms, and for those who do, the amount and how often the symptoms happen will be different for each women. In most cases these symptoms are mild and are not harmful, but you should contact the clinic if any of the symptoms become severe or too uncomfortable. The minor symptoms associated with the study pills usually go away within six months of starting the study pills.

In rare cases, serious problems can occur from use of hormone pills, including cancer of the breast, uterus, stones in the gallbladder, or blood clots in the legs or lungs. [Show participant the table on the HRT consent.] However, the health care professionals here are very concerned about your safety and will be very careful with the procedures and will monitor regularly for early signs of more serious problems.

Remember, you can call the CC at any time throughout the study if you're having any problems or if you have any questions. What questions do you have?"

Figure 4.13
DM Consent Script

Suggested Script for Dietary Modification Consent:

"There are several points that I would like to review with you about the Dietary Program. I'm sure you have several questions about this part of the study, and this may answer some of those questions.

First, as with all parts of the Women's Health Initiative, taking part in the Dietary Program is completely voluntary and you may drop out at any time. You may choose to answer or not to answer any questions on the study forms. Any information that you give is completely confidential and will only be seen by WHI staff, no one else. All of your answers are grouped with the answers of other women in the study, and only this grouped information is released. Neither your name nor any other type of identifying information will be released in any reports.

In order to take part in the Dietary Program, there are more tests that you will have. These include a mammogram, an electrocardiogram or EKG a phyisical examination of your breasts by a WHI clinician.

Women in the Dietary Program will be placed by chance to one of two groups: a "Dietary Change" group or a "Comparison" group. A computer will make the selection. No one knows beforehand who will be in each group or has anything to do with what group you get. Before you sign up you must be willing to take part in either group, whether it is the Dietary Change group or the Comparison group. Both groups are equally important to the results of the study since everything we learn will come from comparing the groups. Once you begin, no one can take your place in the study group to which you have been assigned.

If you are placed in the Dietary Change group, you will attend regular group meetings. At these meetings you will receive advice on how to reduce the amount of fat that you eat and increase your servings of fruits, vegetables, and grains. These meetings will be held once a week for the first six weeks, every two weeks for the six weeks after that, and once a month for the next nine months. The meetings last about two hours. If you cannot attend a group session, you will be asked to make it up. In addition, you will be asked to keep careful records of the foods you eat as you change your eating patterns. That is what is required for the first year of the study. The total time this will take during the first year is about 36-40 hours in meetings plus travel time to the clinic. In addition, you will spend about one hour per day in home activities and recording the foods you eat. Starting in the second year and until the end of the study (about 8-12 years), you will attend group meetings four times a year.

If you are placed in the Comparison group, you will not be asked to make changes in what you normally eat. You will be contacted every six months, attend CC visits once a year, and will spend less than 10 hours a year in study activities.

Whether you are placed in the Dietary Change group or the Comparison group, you will be contacted every six months and make follow-up visits to the CC every year. At these visits, you may be asked to keep careful records of the food you eat and how they are prepared. There is a small chance someone might call you to ask about what you ate the day before. In addition, measurements and lab procedures similar to the screening tests you have already taken will be done. These may include pulse, blood pressure, height, and weight. You may also have clinical breast exams, electrocardiogram or EKG measurements of your physical abilities, and blood draws. There is a small risk of a bruise or slight infection at the site of the blood draw; however, the risk is no greater than if your blood were drawn in a doctor's office. You will be asked to have a mammogram at least every two years. A mammogram uses radiation, which may slightly increase the risk of developing breast cancer. Scientists of the WHI and the National Cancer Institute believe that this small risk is outweighed by the benefit of finding breast cancer early. Mammogram every one to two years are recommended for all women in your age group. The health care professionals here are very concerned about your safety and will be very careful with these procedures. There are no known risks associated with making the dietary changes.

Remember, you can call the CC at any time throughout the study if you're having any problems or if you have any questions. What questions do you have at this time?"

Figure 4.14
OS Consent Script

Suggested Script for Observational Study Consent:

"There are several points I would like to go over with you about the Observational Study. I'm sure you have several questions about this part of the study, and this may answer some of those questions.

First, I'd like to tell you about the purpose of the Observational Study. Many important women's health issue issues will be studied in this part of the WHI. We are interested in learning about what causes disease in women. We'd also like to see what health habits affect a woman's risk for getting heart disease, cancer, or broken bones.

We're hoping you will join the Observational Study. Some women join because they don't want to be in the other WHI programs, or because their screening tests showed that this part of the study would be the best choice. As with all parts of the WHI, taking part in the Observational Study is completely voluntary and you may drop out at any time. Any information that you give is completely confidential and will only be seen by WHI staff and no one else. All of your answers are grouped with the answers of other women in the study, and only this grouped information is released. Neither your name nor any other type of information about you will be given in any reports.

Women in the Observational Study will all be asked to fill out several questionnaires and forms at the start of the study. You may choose to answer or not to answer any questions on the study forms. Then, every year for the next eight to twelve years, you will be mailed forms like some of the one you have already filled out. These forms will ask questions about your health and any medical problems that may have happened in the last year. You will be given a stamped envelope to mail the forms back to the CC after you finish them. Once you join the study no one can take your place, so we'd like you to try to stay with the study for the entire time of the study.

In three years you will come back to the CC for a follow-up visit. At this visit, measurements and lab tests, like the screening tests you have already had, will be done. Your height, weight, waist and hips will be measured again, and your pulse and blood pressure will be taken. We will also draw a small amount of your blood for testing. There is a small risk of a bruise or infection when blood is drawn, but it is no greater than if your blood were drawn in a doctor's office. There are no other known risks associated with any of the things you will be asked to do.

A small number of women in the Observational Study will be asked to come in for another visit soon after the initial and three-year visit to repeat the same measures. The purpose of this visit is to help us learn about the precision of these measures.

Every year you will also be sent a newsletter. This newsletter will give you information about the progress of the study and will help us know that we still have your correct address.

Remember, you can call the CC at any time throughout the study if you're having any problems or if you have any questions. Do you have any questions now?"

Figure 4.15
Suggested Script for Blinded Study Medication Dispensation

Participant:

"How will I know which study pill I'm taking?"

Staff:

"You will not know which study pill you are taking and neither will we. If you have not had your uterus removed, you will be taking either a combination of progesterone and estrogen; or a placebo pill which means no active medicine. If you have had your uterus removed you will be taking either estrogen or placebo. The selection of which pill you take is done by chance much like the toss of a coin, selected by a computer."

Participant:

"Will I be taking a placebo pill at first?"

Staff:

"It's important to understand that this program is a research study. Because this is a study, there may be times that you are placed on a placebo pill for part of the study, and I will not be able to share with you when that time will be. There is also a chance you may be taking a placebo for the entire study."

If the participant still seems anxious about this information:

Staff:

"You seem anxious or concerned about what I just told you." (Hopefully, giving the participant time and patience to voice her concern will decrease her fears. However, if the participant still shows a lot of problem with this issue, it may be wise to choose not to enroll her into this portion of the study and interest her in one of the other choices.)

You should never disclose single- or double-blind information to a participant. As long as you explain this information as stated above, you are not lying to the participant and you are protecting the importance of the blinding process at all times.

It is very important to disclose this information before she signs the consent form. Then, as these questions arise again in six months or two years from now, the participant can again be reminded of what was initially said. Being consistent in your clinic (with all staff explaining this the same way using the same terminology) will help maintain the trust and comfort you want your participants to have.

Keep in mind that the randomization visit (SV3) means more to the CC than it does to the participant. The participant believes that she is in the study from the moment of signing the consent form and complying with your instructions to proceed. If the staff does not focus on the other changes that occur at this visit, the participant won't either, especially when a new bottle is dispensed.

4.6.5. Blinding Considerations and Recommendations

Blinding in the WHI involves several special issues that are unique to this set of trials. It is the intent of the WHI investigators and staff to minimize bias in trial results, thus necessitating blinding of participants and staff wherever possible. Because of the staffing configurations present in WHI CCs, maintaining staff blinding throughout the trial may pose a significant challenge.

4.6.5.1. Definitive and Effective Unblinding

Unblinding for HRT, DM, or CaD may occur definitively or effectively:

- Definitive unblinding occurs when the CC Unblinding Officer enacts the database unblinding function for HRT or CaD or when CC staff view specific database information (either in documents or on the computer screen) for DM.

- Effective unblinding occurs when a staff member or participant makes an educated guess about a participant's treatment (e.g., because of vaginal bleeding).

HRT is a double-blinded trial. The goal is to keep all CC staff, investigators, and participants blinded to study arm for the duration of the study. However, because of the signs and symptoms associated with female hormone use, there will be situations in which unblinding occurs, either definitively or effectively. All efforts will be made to keep the occurrences of unblinding to a minimum, while ensuring that participant safety is kept as a high priority.

DM is by its nature an unblinded trial. However, for unbiased ascertainment and adjudication of primary, subsidiary, and intermediate outcomes, it is essential to keep staff involved in ascertainment or adjudication of any of these outcomes blinded to trial arm. Because of the sharing of clinical duties among CC staff, this means the CC staff may also be definitively or effectively unblinded for DM women. However, the goal is that all CC staff other than the group nutritionists and dietary session staff should be blinded to treatment arm for the DM.

The CaD is a double-blinded trial. The goal for this trial is also to ensure complete blinding throughout the trial. Definitive unblinding should be extremely rare in this trial, although there may be a constellation of symptoms associated with CaD use that may result in participants or CC staff being effectively unblinded.

There are several ways in which definitive or effective unblinding can occur within specific WHI study components:

- HRT

  Definitive unblinding for investigation of symptoms/signs of pathology: Careful algorithms have been devised by WHI medical staff for the evaluation of symptoms such as vaginal bleeding. Each CC identifies an Unblinding Officer, who communicates unblinding results directly to the CC Consulting Gynecologist. The Consulting Gynecologist after becoming definitively unblinded, will direct the blinded CC staff as to appropriate management, thereby preserving definitive blinding of key CC staff (but not necessarily preserving effective blinding).

  Effective unblinding of CC medical staff doing gynecological exams: Because of the vulvar, vaginal, and cervical changes caused by female hormones, CC staff performing pelvic exams may become effectively unblinded to "active" or "inactive" study medications.

  Effective unblinding of participants and staff because such as vaginal bleeding: Because placebo study medication should not cause vaginal bleeding, women starting study pills who develop vaginal bleeding may become effectively unblinded to "active" or "inactive" study pills.

Adverse Effects: Definitive unblinding because of "serious adverse effects" may occur, such as in the case of primary care provider asking for treatment assignment of the management of certain medical conditions. In this instance, the Consulting Gynecologist may decide that only the primary care provider needs to be given the treatment arm information.

- DM

  Randomization: At SV3 the participant is randomized by CC staff member and receives a randomization report. The staff member performing the randomization will be unblinded, as will any staff member who is privy to the report at that visit or any report that includes DM treatment assignment as a data item.

  Participant in DM groups located at main clinic facilities: Effective unblinding of DM intervention participants may occur if they are seen by CC staff coming in group to meetings or if they call to cancel or reschedule intervention sessions.

  DM intervention nutritionists' files: The Group Nutritionists maintain files on all DM intervention participants. If these files are kept with other components of participant files or in any centrally accessible location, other CC staff may become definitely unblinded.

  Follow-up visits and activities: DM participants, if not warned otherwise, may talk about group issues at their follow-up clinic visits, resulting in effective unblinding of CC staff.

  Outcomes: If participants discuss their study involvement with their primary care providers, outcomes staff perusing medical files may become effectively unblinded if such discussions are filed. Participants also may call the CC between regularly scheduled visits to report outcomes, and may report their study arm at the same time, thereby effectively unblinding staff members.

4.6.5.2. Strategies for Maintaining Blinding

The following are required CC activities to maintain blinding:

- Ask DM participants not to reveal their randomization assignment to CC staff.

- Group Nutritionists are responsible for reminding/rescheduling DM Intervention participants and have access to DM Intervention files.

- Unblinding is requested by the Consulting Gynecologist and carried out by the Unblinding Officer. The Clinic Practitioner (CP) should note in the participant's contact notes that an unblinding occurred and the action recommended by the Consulting Gynecologist. However, the treatment assignment information provided to the Consulting Gynecologist is not provided to the CP or written anywhere on the participant's file. The Consulting Gynecologist should keep a brief written record of the circumstances, separate from the participant's file with her name, ID number, pertinent clinical information, and treatment recommendations and rationale.

- The same CC procedures are used for follow-up contacts (semi-annual or annual) with both DM Intervention and Control participants.

- Clinical Center staff who have authorized access to either the DM Intervention files or the HRT files are not involved in outcomes adjudication (assigning outcomes diagnoses).

- Clinical Centers document local blinding and unblinding procedures for HRT, DM, and CaD.

- Participants and CC staff will be asked at the close-out visit which arm they thought they were in.

The following are strongly recommended CC activities to maintain blinding:

- Prepare separate participant files for HRT forms (e.g., symptoms on *Forms 10* and *53*, gynecological exams on *Forms 81, 82,* and *83*, medication changes on *Form 54*) and contact notes and for DM Intervention forms (e.g., session data on *Forms 63, 64,* and *65* and session feedback on *Forms 70, 71,* and *72*) and contact notes.
- Follow-up dietary assessment and clinical assessment staff do not randomize participants to DM and do not have access to participants' DM Intervention or HRT files.
- Participants' general files should contain no notations, special colors, or special labels about DM intervention status. Database reports viewed by staff other than Group Nutritionists or DM Intervention support staff should have DM assignment blacked out.
- Develop signs and remind DM participants at follow-up visits not to tell CC staff their DM assignment.
- HRT and DM Intervention files should be kept separate from the participant's general file, preferably with access available only to authorized staff.
- Clinical Centers should identify a route to DM sessions that bypasses staff not involved in the DM Intervention.
- Clinical Center staff with authorized access to DM Intervention or HRT files should not be involved in outcomes ascertainment (requesting and compiling outcomes documentation).
- Outcomes ascertainment should be accomplished by a trained data entry or medical assistant staff person.
- Clinical and dietary assessment staff should not be involved in outcomes ascertainment.

- Do not file *Form 7 - Participant Status* in the participant's general file if unblinding would result (e.g., for DM participants), or as appropriate, file the *Form 7* in an area of the participant file to which the staff generally does not have access. Document in the contact notes that the participant's status has changed and indicate that a *Form 7* has been completed.

Figure 4.16
HRT Enrollment Pill Count To Pill Weight Conversion Chart

Number of Pills Remaining in Bottle	Weight in Grams to Enter into WHILMA
1	0.3
2	0.5
3	0.8
4	1.0
5	1.3
6	1.5
7	1.8
8	2.0
9	2.3
10	2.6
11	2.8
12	3.1
13	3.3
14	3.6
15	3.8
16	4.1
17	4.3
18	4.6
19	4.8
20	5.1
21	5.4
22	5.6
23	5.9
24	6.1
25	6.4

Number of Pills Remaining in Bottle	Weight in Grams to enter into WHILMA
26	6.6
27	6.9
28	7.1
29	7.4
30	7.7
31	7.9
32	8.2
33	8.4
34	8.7
35	8.9
36	9.2
37	9.4
38	9.7
39	9.9
40	10.2
41	10.5
42	10.7
43	11.0
44	11.2
45	11.5
46	11.7
47	12.0
48	12.2
49	12.5
50	12.8

Section 4
Screening

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