SECTION 15

MEDICATIONS (STUDY PILLS)

INTRODUCTION

Clinical Center (CC) staff members dispense study pills to participants in Hormone Replacement Therapy (HRT) and Calcium and Vitamin D (CaD) components of the Clinical Trial (CT) and provide instructions on how to take the daily study pills.

McKesson BioServices Corporation (McKesson) receives the HRT and CaD pills from the drug manufacturers, inventories, stores and labels the bottles with unique bottle numbers, and ships the labeled bottles to the CCs. Enrollment pills for HRT are packaged in bottles of 50 pills. Study pills for the treatment arms after randomization are packaged in bottles of 215 pills, and open label hormones in bottles of 100. Calcium and Vitamin D study pills are packaged in bottles of 215 chewable tablets and 430 swallowable pills.

The CCs store a 1- to 2-month supply of HRT and CaD bottles, use WHILMA to select the appropriate bottles to dispense to each participant, label the bottles with the participant's name and ID number, dispense the bottles to the participant at regularly scheduled appointments or as needed, record receipt of returned bottles, and assess the participant's study pill adherence.

This section gives a description of the medication storage facility at each CC; the procedures for receiving, selecting, labeling, and dispensing the medications to participants; the procedures for assessing the participant's adherence to taking the study medications; the procedure for shipping returned study pill bottles to McKesson; and procedures for reporting serious adverse experiences.

15.1 Medications (Study Pills)

15.1.1 HRT Component

Wyeth-Ayerst (W-A) supplies all the HRT enrollment and study pills for the Women's Health Initiative (WHI).

15.1.1.1 Enrollment Pills

The drug manufacturer provides enrollment pills in bottles of 50 pills.

McKesson labels and ships HRT enrollment bottles to CCs in boxes labeled "HRT ENROLLMENT." Each box contains 36 bottles.

15.1.1.2 HRT for Randomized Participants

The following four types of HRT study pills are provided:

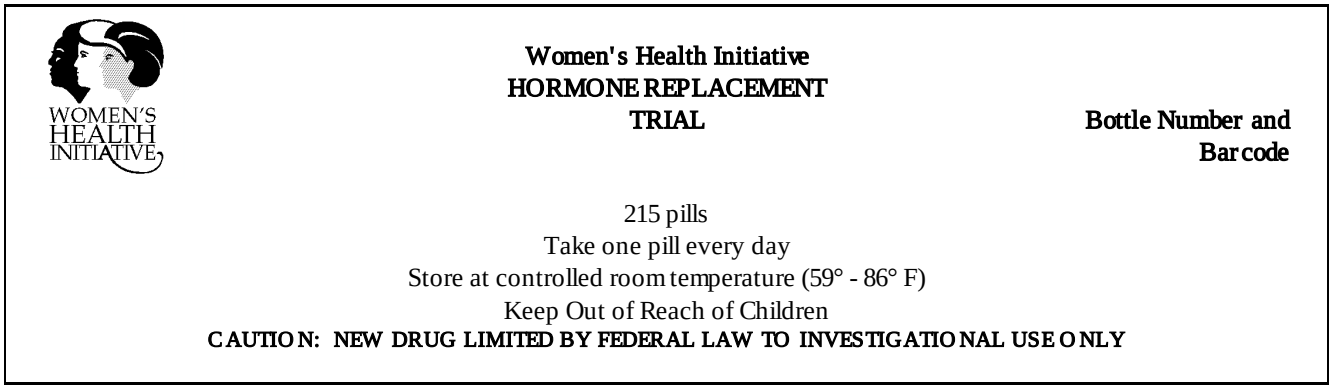
- ERT pills: conjugated equine estrogen (CEE) 0.625 mg
- ERT placebo pills: conjugated equine estrogen (CEE) placebo
- PERT pills: conjugated equine estrogen (CEE) 0.625 mg plus medroxyprogesterone (MPA) 2.5 mg
- PERT placebo pills: conjugated equine estrogen (CEE) plus medroxyprogesterone (MPA) placebo

See *Tables 15.3 - WHI Placebo Ingredients (PERT Placebo)* and *15.4 - WHI Placebo Ingredients (ERT Placebo)* for listings of HRT placebo study pill contents.

The HRT study pills (ERT, PERT and their corresponding placebos) are supplied in bottles of 215 pills. McKesson labels each bottle with the sample label shown in *Figure 15.1 - Sample HRT Label*.

McKesson ships the labeled HRT study pill bottles to CCs in boxes labeled "HRT" and either "hysterectomy" or "no hysterectomy." Each box contains 60 bottles with a specified proportion of ERT and ERT placebo in the "hysterectomy" box and PERT and PERT placebo in the "no hysterectomy" box.

Figure 0-1
Sample HRT Label



15.1.1.3 Open Label Study Pills

Open label hormones are supplied in commercially-labeled bottles of 100 pills. The commercial labels contain the hormone name and dose. McKesson ships these bottles to the CCs in boxes labeled "HRT Open Label" and the corresponding type of study pills. Each box contains 5 bottles.

The following types of open label hormones are supplied:

- conjugated equine estrogen (CEE) 0.3 mg
- conjugated equine estrogen (CEE) 0.625 mg
- medroxyprogesterone (MPA) 2.5 mg
- medroxyprogesterone (MPA) 5 mg
- medroxyprogesterone (MPA) 10 mg

15.1.2 CaD Component

The drug manufacturer provides the following two types of CaD study pills:

Mint-flavored chewable tablets

- Calcium carbonate containing 500 mg elemental calcium plus vitamin D_3 200 IU or placebo
- Each bottle contains 215 CaD study pills
- Each box contains 24 bottles

In addition to the regular cartons of chewable CaD study pills, a second configuration type called "BCaD" is available. The purpose of the BCaD is to prevent an individual clinical center's chewable CaD inventory from becoming "out of balance." Inventory is considered out of balance when a clinic has several partially-used cartons open but is unable to dispense from any of them.

BCaD cartons contain 24 bottles of chewable CaD. Each bottle contains 215 CaD study pills. The study pills in the BCaD cartons are identical to those in the regular CaD bottles. Procedures described elsewhere in this section for the dispensation, adherence collection and disposal of chewable CaD pills also apply to pills taken from BCaD cartons.

Swallowable pills

- Calcium carbonate containing 500 mg elemental calcium plus vitamin D_3 200 IU or placebo (reformulated from 125 IU to 200 IU Vitamin D in Spring 1998)
- Each bottle contains 430 CaD study pills
- Each box contains 48 bottles

See Table 15.6 – WHI Placebo Ingredients (CaD Placebo) for a listing of CaD placebo ingredients.

McKesson labels each bottle with the sample CaD label shown in *Figure 15.2 - Sample CaD Labels (a. Chewable Tablets, b. Swallowable Pills)*. McKesson ships supplies of CaD to CCs. Each box of CaD study pills has a specified proportion of active and placebo study pills.

Figure 15.2
Sample CaD Labels
a. Chewable CaD Tablets

Women's Health Initiative
CALCIUM/VITAMIN D TRIAL

Bottle Number and Barcode

215 Tablets
Chew One Tablet 2 Times a Day with Food
Store at Controlled Room Temperature (59° - 86° F)
Pkg/Dist: McKesson BioServices, Rockville, MD 20850
Keep Out of Reach of Children
CAUTION: NEW DRUG LIMITED BY FEDERAL USA LAW TO INVESTIGATIONAL USE

b. Swallowable CaD Pills

Women's Health Initiative
CALCIUM/VITAMIN D TRIAL

Bottle Number and Barcode

430 pills
Do not chew
Take One Tablet 2 Times a Day with Food. "Do Not Chew"
Store at Controlled Room Temperature (59° - 86° F)
Pkg/Dist: McKesson BioServices, Rockville, MD 20850
Keep Out of Reach of Children
CAUTION: NEW DRUG LIMITED BY FEDERAL (USA) LAW TO INVESTIGATIONAL USE

15.1.3 Child-Resistant Caps (Required)

Routinely offer participants a non-child resistant cap each time study pills are dispensed. All HRT and CaD bottles come with child-resistant caps. Embedded within each of these caps is a non-child resistant cap. Follow the procedures below if a participant requests a non-child-resistant cap.

- Ask the participant to sign and date a statement requesting a non-child-resistant cap. A participant needs to complete this form one time, not each time you give her a new bottle (see *Figure E.5.9 - Model Statement for Non-Child-Resistant Cap* for a sample statement).
- Remove the child-resistant cap from the bottle before dispensing and replace it with a non-child-resistant cap.
- File the signed statement in her participant file.

Removing the Child-Resistant Portion of a Study Pill Cap

Use the following directions to remove the child-resistant portion of the full cap assembly:

1. Take the cap off a bottle to see the two parts. The outer cap is made of white plastic (the part you had to push down while turning to remove the cap). Inside that cap is what looks like a liner, made of a less opaque white plastic.

2. Screw the cap back on the bottle.

3. The outer white plastic cap can be flipped off easily, using a strategy similar to opening a soda bottle with a bottle opener. Use a cap remover (purchased from a pharmaceutical supply house) or wedge the white safety cap into the handle of a file drawer or door, push down on the bottle itself, and the white top should pop off.
4. The portion of the cap that remains on the bottle (non-child-resistant portion) can be twisted on and off in the usual manner.
5. If you want to replace the child-resistant portion of the cap, just place it over the portion remaining on the bottle and push down firmly--it helps to get your weight on it!
6. CAUTION: Do not use a hand tool, such as a screwdriver, to try to pry the top off. The child-resistant portion of the cap is meant to be popped off, not pried off. Clinical Centers may want to purchase specialized tools for this purpose.

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15.2 Study Pill Storage Area (Required)

Each CC is responsible for maintaining a secure area for storing both HRT and CaD study pills. This storage area could be a small room with shelves and counter space or a larger multi-purpose room with locking cabinets for the boxes and nearby working counters or tables.

15.2.1 Storage Area Specifications

Each CC should have a secure storage area. This room should not be open to the public. The storage room should be locked when not in use. The area should be adequate to contain the following:

- A 2-month supply of all HRT and CaD study pills. Each HRT enrollment and open-label study pill box is 12" wide x 12" deep x 4.5" high. HRT randomized study pill boxes are 12" wide by 20" deep x 4" high. Chewable CaD study pill boxes are 23" long x 16" wide x 8" tall and swallowable CaD study pill boxes 19 3/8"wide x 12 7/8" deep x 6 1/2" high (approximately). See *Section 15.3.1 - Minimum Inventory (Required)* for minimum number of each type of study pills to store.
- Scale for weighing bottles and study pills.
- Adequate counter space for all activities related to study pill handling.

15.2.2 Storage Area Organization

It is helpful to keep each distinct study pill type in separate areas within the storage room. The room can be separated in the following distinct areas:

HRT: Enrollment pill bottles
Randomized study pill bottles for "hysterectomy"
Randomized study pill bottles for "no hysterectomy"
Open label hormone bottles:
CEE 0.3 mg
CEE 0.625 mg
MPA 2.5 mg
MPA 5 mg
MPA 10 mg
Returned or discarded HRT study pills

CaD: Randomized chewable study pill bottles, including bottles from BCaD cartons
Randomized swallowable study pill bottles
Returned or discarded CaD study pills

15.2.3 Storage Area Work Space

The storage area should be equipped with a work space to:

- Unpack study pill shipments from McKesson and process corresponding paperwork.
- Accommodate one PC connected to CC's LAN (or have one close by).
- Select study pill bottles during participant's visit or contact and enter dispensing and adherence information in the database.
- Weigh study pills/bottles for adherence.
- Package and mail study pill bottles to participants when necessary.
- Package and ship returned, expired, damaged or other unusable bottles to McKesson, as appropriate.
- Maintain records of study pill shipments sent and received.

15.3 Study Pill Inventory Maintenance

15.3.1 Minimum Inventory (Required)

Clinical Centers should maintain a 1- to 2-month supply of all HRT and CaD study pills. The minimum supply level for each is:

Type		Minimum
HRT	Enrollment pill boxes	1 box of 36 bottles
	Randomized HRT boxes:	
	hysterectomy	1 box of 60 bottles
	no hysterectomy	1 box of 60 bottles
	Open label hormone boxes:	
	conjugated equine estrogen (CEE) 0.3 mg	1 box of 5 bottles
	conjugated equine estrogen (CEE) 0.625 mg	1 box of 5 bottles
	medroxyprogesterone (MPA) 2.5 mg	1 box of 5 bottles
	medroxyprogesterone (MPA) 5 mg	1 box of 5 bottles
	medroxyprogesterone (MPA) 10 mg	1 box of 5 bottles
CaD	Randomized CaD boxes	
	chewable study pills	1-3 boxes of 24 bottles
	BCaD chewable study pills	2 boxes of 24 bottles
	swallowable study pills	1-2 boxes of 48 bottles

Determine the study pill supply needed based on your CC's randomization rates and follow-up contact schedule.

Note that you may need to open a new box of study pills before dispensing all the bottles in a box that is currently open. Monitor your study pill supply and order more boxes from McKesson before you complete one box. For CaD you also need to allow for the approximate 2-week delivery time.

Note that maintaining BCaD inventory requires an additional step: when <u>any</u> BCaD carton in inventory drops to eight bottles or less, contact McKesson and order a new BCaD carton to replace it. Do this even if you have other BCaD cartons with more than eight bottles. In your order to McKesson, reference the 6-digit carton ID number of the BCaD carton that you are replacing. McKesson can't fill BCaD orders without this carton ID number.

Run a *Drug Inventory Report* (*WHIP 0032*) from WHILMA on a regular basis (at least quarterly) and resolve any discrepancies between the report and your actual inventory. (See *Table 15.1 - List of Discrepancies Between Drug Inventory Report and Actual Inventory, Possible Causes, and Actions to Take)*.

15.3.2 Request Study Pills from McKesson (Required)

McKesson ships study pill bottles to CCs in response to orders placed by the CCs. Each CC is responsible for updating its projections and maintaining adequate supplies based on a projected 1- to 2-month period.

To request additional study pills from McKesson:

- Estimate the CC's study pill needs for the next 1- to 2-month period.
- Send the request to McKesson via DaVinci eMAIL (use phone or fax if eMAIL is not convenient). (See the WHI Directory for phone numbers and addresses.)
- Telephone emergency requests to McKesson and follow up with an eMAIL message or fax
- If ordering BCaD from McKesson, reference the carton ID number of the carton you are replacing as described in *Section 15.3.1 – Minimum Inventory*.

Table 15.1
List of Discrepancies Between Drug Inventory Report (WHIP 0032) and Actual Inventory, Possible Causes, and Actions to Take

Discrepancy	Possible Cause	Action
According to the report, a bottle is neither dispensed nor disabled, but is missing from inventory.	1. Bottle was given to a participant without using WHILMA to select the bottle number (e.g., selection of enrollment bottle was not recorded on backup form or has not yet been key-entered). 2. Bottle selection was made using WHILMA but transaction was not committed by pressing F10 in WHILMA. 3. Staff person key-entered the bottle number (instead of scanning the barcode on the bottle label) and made an error in the key-entry. 4. Bottle was discarded due to damage or loss but was never disabled in WHILMA. 5. Barcode label on bottle was incorrect or bottle was in incorrect position in box.	Make a note of the dispensation dates of other recently-dispensed bottles from that carton. Using the randomization log, clinic appointment schedule, and contact notes from participant files, try to determine which participant received the missing bottle. Confirm the bottle number with the participant before contacting the CCC Data Coordinator to make any changes in WHILMA. If you determine that the bottle was discarded due to damage or was lost before it could be dispensed, enter the date discarded as the "disable date" in the Medication Inventory Management screen of WHILMA.
A bottle listed as dispensed on report is still in inventory.	1. Staff person selecting bottle key-entered the bottle number instead of scanning the barcode on the bottle label and made an error in key-entry.	Review file of participant to whom bottle was supposedly dispensed. Contact participant if necessary to verify the correct number of the bottle dispensed. Contact CCC Data Coordinator to correct the data in WHILMA.

15.3.3 Receiving Study Pills (Required)

Each CC should designate a staff member to be responsible for unpacking and storing the pills. Upon receiving a shipment from McKesson:

- Verify the contents of the carton with the enclosed packing slip.
- Send an email message to McKesson acknowledging receipt of the shipment.
- Record receipt of boxes in WHILMA following data management instructions (see *Vol. 5 – Data System, Section 7.3.3.1 – Conducting Study Medication Inventory*).
- Store the boxes in the designated location in the medications storage area with the labels showing.

15.3.4 Returning Study Pills to McKesson (Required)

15.3.4.1 Returning HRT Study Pills

Ship all HRT study pills returned by participants to McKesson for disposal. At times, McKesson will also request return of unused or expired pills. McKesson has assumed the responsibility for proper disposal of the unused pills as required by the Investigational New Drug (IND) requirements. The pills are toxic in high doses and are thus considered "hazardous waste."

Return only the pills; discard the empty bottles (after blacking out the participant's name on the label).

1. Label an empty study pill carton or other cardboard box with "Return Study Pills." Place a heavy-duty plastic bag (must be 1.0 mil thickness or greater) or plastic container in the box. Do not use plastic bags that are sealed with a zip lock mechanism.
2. Place the box on a counter in a secure location.
3. After weighing returned pills [see *Section 15.6.2.2 – Medications (Study Pills)*], place the pills in the plastic bag (do not mix HRT with the two forms of CaD pills). Do not fill the bag with more than 25 pounds of discarded pills.
4. When the bag is no more than three quarters full or 25 pounds in weight (whichever comes first), fold the top of the bag down twice and seal with heavy-duty tape such as mailing tape or duct tape. Do not use masking tape or cellophane tape for this purpose.
5. Put the sealed bag into another heavy plastic bag and seal the second bag with heavy-duty tape.
6. Write "discarded HRT" on a self-adhesive label and place the label securely on the outer bag.
7. Pack the bag into a heavy-duty corrugated cardboard container. It is acceptable to use a used cardboard carton for this purpose if the carton is in good condition. Do not use a carton that shows signs of wear or weakness from previous use.
8. Weigh the packed carton to make sure that it does not exceed 25 pounds.
9. Use heavy-duty tape and seal the carton well so that it will not break open during shipment. Label the carton with a pre-printed McKesson address label.
10. Mark the CC name and return address clearly on the outside of the carton.
11. Ship the cartons of returned pills to McKesson. Use the least expensive method (e.g., regular mail or UPS) to ship the cartons.
12. McKesson will ensure proper disposal of the pills.

15.3.4.2 Returning CaD Study Pills

Clinical Centers should dispose of CaD study pills appropriately. You can return study pills to McKesson or dispose of returned CaD study pills at your CC following the state and institutional regulations to ensure safety. In addition, each CC disposing of CaD study pills must account for the number of each type of study pills discarded. This is required by the Investigational New Drug (IND) agreement.

1. Determine and document your state, local and/or institutional requirements for disposal of CaD study pills. Develop a log to track chewable and swallowable CaD study pill disposal separately. An example of a CaD disposal log is given in *Figure 15.3 – CaD Disposal Log Example*.

   If a CC does not have the resources to provide for safe and legal disposal, or chooses to continue to mail the returned CaD study pills back to McKesson, do so via surface or other low cost mailing system. Follow the instructions in *Section 15.3.4.3 – Returning Discarded CaD Pills to McKesson* when preparing the pills for shipment.

2. CaD "chewable" and "swallowable" study pills must be accounted for separately. Use the following procedures to account for and dispose of CaD study pills:
   - Label one box "Chewables" and the second "Swallowables." Also record an "identifier" on each box (example: #1 Chewables).
   - Place a heavy-duty plastic bag(1.0 mil thickness or greater) or plastic container in each of the boxes. Do not use plastic bags that are sealed with a zip lock mechanism.
   - Weigh each of the boxes and record the weights on your logs (columns A and B).
   - Assess adherence on CaD study pill bottles as directed in *Vol. 2, Section 15.6.2.2 – Bottle Weighing Procedure*.
   - Place CaD chewable tablets and swallowable pills in the plastic bags lining the appropriate disposal boxes as described in *Section 15.3.4.1 – HRT Study Pills*.
   - When a disposal box full, weigh the box. Record this weight in your log (column C).
   - Calculate the weight of the pills by subtracting column B from column C. Record this value in your log (column D).
   - Calculate the estimated number of pills you are disposing by multiplying the value in column D by 338. (1 kg chewables = 338 tablets, 1 kg swallowables = 791 pills). Record the number of pills or tablets on your log (column E).
   - Record the date the disposal box is removed from your CC (column F).

3. Archive the CaD Disposal Logs for future reference (see *Figure 15.3 – CaD Disposal Log Example*).

15.3.4.3 Returning Discarded CaD Pills to McKesson

If you choose to return the pills to McKesson for disposal, follow these steps for preparing the returned pills for shipment:

- When a disposal box is no more than three quarters full or 25 pounds in weight (whichever comes first, remove the plastic liner bag with the pills in it from the box.
- Fold the top of the bag down twice and seal with heavy-duty tape such as mailing tape or duct tape. Do not use masking tape or cellophane tape for this purpose.
- Put the sealed bag into another heavy plastic bag and seal the second bag with heavy duty tape.
- Write "discarded CaD" on a self-adhesive label and place the label on the outer bag.

- Pack the bag into a heavy-duty corrugated cardboard container It's acceptable to use a used cardboard carton for this purpose if the carton is in good condition. Do not use a carton that shows signs of wear or weakness from previous use.
- Weigh the packed carton to confirm that it doesn't exceed 25 pounds.
- Use heavy-duty tape and seal the carton well so that it will not break open during shipment. Label the carton with a pre-printed McKesson address label.
- Mark the CC name and return address clearly on the outside of the carton.
- Ship the cartons with returned pills to McKesson. Use the least expensive method (e.g., regular mail or UPS) to ship the carton.

Figure 15.3
CaD Disposal Log Example

Box (A)	Empty Box Weight (B)	Full Box Weight (C)	Weight of Pills (D) [C - B]	Calculated Number of Pills (E) [D x 338] (chewable) or [D x 791] (swallowable)	Date of Disposal (F)
#1 (chewables)	10 kg	56 kg	46 kg	46 x 338 = 15,548	2/17/97
#2 (swallowable)	10 kg	30 kg	20 kg	20 x 791 = 15,820	3/16/98

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15.4 Study Pill Dispensing (Required)

Dispense study pill bottles to participants at regularly scheduled contacts. You may also dispense study pill bottles through the mail as needed (see *Section 15.5 - Selecting and Dispensing Problems (Required)*. All study pill bottles must be selected in WHILMA.

Clinical Centers should be familiar with and follow state and institutional regulations regarding dispensing of medications.

15.4.1 Selecting and Dispensing Enrollment HRT Bottles at Screening Visit 2 (SV2) (Required)

Select and dispense one enrollment pill bottle (or more, if necessary) and supporting materials to each participant interested in HRT at SV2. Supporting materials include a 7-day pill organizer, *Form 53 - HRT Calendar* (if she has a uterus), and an *HRT Handbook*.

15.4.1.1 Preparation (Required)

Ensure that a bottle label is in the participant's file.

- The bottle label has the CC name and phone number, the participant's name, and the participant's ID number with corresponding barcode label. These labels are usually printed after the participant has been assigned a participant ID number and has signed an HRT Consent Form (see *Vol. 5 - Data System, Section 7.3.3.2 - Printing Bottle Labels*).
- Do not attach the label to a bottle at this time.

15.4.1.2 Selecting and Dispensing at SV2 (Required)

After you determine a participant's interest in participating in HRT, select the HRT enrollment bottle as described in *Vol. 5 - Data System - Section 7.3.3.3 - Selecting Run-In (Enrollment) HRT Bottles.*

If desired, print out a *Dispensation Report* (*WHIP 0232)* and file it in the participant's file.

Ask the participant if she prefers a non-child resistant cap, and obtain the proper consent, as appropriate.

Give the bottle to the participant. Remind her to bring the bottle back at the next visit.

> *Note*: Give the enrollment pill bottle to the participant **only after** you have labeled the appropriate bottle with the participant's name and ID number.

Give her the *HRT Handbook* (see *Appendix F - Required CC Participant Materials*), the 7-day pill organizer, and *Form 53 - HRT Calendar* (if she has a uterus). Explain:

- Study pill instructions, using the *HRT Handbook*.
- What she could expect when she takes the pills, using the *HRT Handbook*.
- How to remember to take pills, using the pill organizer.
- How to record any bleeding, using *Form 53 - HRT Calendar* (as appropriate).

See Section 5.2 - Initiating the HRT Intervention at SV2 for further reference.

If screening visit 3 (SV3) is delayed to the point that the participant runs out of enrollment pills, an additional bottle(s) of HRT enrollment pills can be dispensed as part of her initial enrollment period. See *Section 15.5.4 - Participant's Supply Runs Out (Required)*.

15.4.1.3 Repeat HRT Enrollment Period

If a participant is ineligible due to poor adherence on her first enrollment period, she may undergo a second enrollment period. Use this second enrollment period option only if she has failed (is ineligible) due to adherence to her first enrollment period and there is a reasonable expectation that she will be adherent this second time. WHILMA will ignore the data from the first enrollment period and use only the data from the second enrollment period to determine the participant's adherence to the HRT enrollment pills.

Use the following steps to start the second enrollment period:

- Select a new bottle of HRT enrollment pills.
- In the selection screen, indicate that this is a repeat enrollment period by recording "2" for run-in attempt number. Only record a "2" if the participant has failed adherence to her first enrollment period.
- Dispense the HRT enrollment pills to the participant as you did for the first enrollment period.
- Assess adherence as you did for the first enrollment period.

15.4.1.4 Selecting Enrollment Pills When There are Computer Problems (Required)

If the PC usually used for dispensing is not working, attempt to use another PC to select and dispense HRT enrollment pills. If WHILMA is down, use the back-up form (*Form 955 - Enrollment Pill Dispensing*) and enter the data into WHILMA later. **Always use the scan gun** to enter the bottle number into WHILMA. Only key-enter the ID numbers in the appropriate fields only if you are unable to scan the barcode labels due to a malfunctioning scan gun. If the scan gun is not working properly, contact the CCC Data Coordinator as soon as possible for repair/replacement.

15.4.2 Selecting and Dispensing HRT Bottles at Screening Visit 3 (SV3) (Required)

Dispense one HRT bottle to each participant you randomize at SV3. Ask those participants whose eligibility determination you cannot complete to continue on enrollment pills. The need to continue enrollment pills can occur, for example, if you have not yet received the lab or mammography results. You may need to select and dispense an additional bottle of HRT enrollment pills.

15.4.2.1 Preparation (Required)

Ensure that a barcode bottle label with the CC name and phone number, participant's name, and the participant's ID number is in her file. Do not attach the label with the participant ID number and name to the bottle at this time.

15.4.2.2 Selecting and Dispensing at SV3 (Required)

- Confirm the eligibility status of the participant at SV3. If you cannot complete the eligibility determination of the participant by SV3, return the HRT enrollment pill bottle to her. Dispense an additional HRT enrollment bottle if necessary.
- If the participant is eligible, randomize her to HRT (see *Vol. 5, Section 6 - Eligibility Determination and Randomization*).
- Select the study pill bottles to dispense to the participant as described in *Vol. 5 - Data System, Section 7.3.3.4 - Selecting Study Medications.*
- You must use WHILMA to select the appropriate HRT study pill bottles for the participant. Do not give a participant a bottle if it has not been selected by WHILMA. Dispense the study pill bottle to the participant only after you have labeled the appropriate bottle with the participant's name and ID number. Do not give the bottle to the participant if there is any question whether the transaction has been accepted in WHILMA.

- Print out a *Dispensation Report (WHIP 0232)*, if desired, and file it in the participant's file.
- Give the appropriately-labeled bottle to the participant. Ask her if she prefers a non-child resistant cap. Give her another *Form 53 - HRT Calendar*. Ask her if she needs another *HRT Handbook*. Instruct her on how to take the pills. Remind her to bring the bottle back at the next visit.

15.4.3 Selecting and Dispensing HRT Study Pill Bottles at Semi-Annual and Annual Visits (Required)

HRT study pills may be dispensed at semi-annual contacts or at annual visits. Dispense an annual supply only at annual visits, not at semi-annual visits. Dispensation of HRT study pills should not be made until appropriate safety procedures have been completed. (*See Section 16 - Follow-Up Contacts*). If the participant has had a hysterectomy since the last dispensation, contact the CCC Data Coordinator before dispensing additional HRT study pills (see also *Section 5.5.1 - Management of HRT after Hysterectomy for Non-Cancerous Condition*).

15.4.3.1 Preparation

Before a regularly scheduled semi-annual and annual visit, check to make sure you have bottle labels with the participant ID number and name for the participant's bottle of HRT study pills.

15.4.3.2 Selecting and Dispensing at Follow-up Contacts (Required)

- Select the study pill bottles to dispense to the participant as described in *Vol. 5, Section 7.3.3.4 - Selecting Study Medications.*
- You **must** use WHILMA to select the appropriate HRT study pill bottles for the participant. Do not give a participant a bottle if it has not been selected by WHILMA. Dispense the study pill bottle to the participant **only after** you have labeled the appropriate bottle with the participant's name and ID number. Do **not** give the bottle to the participant if there is any question whether the transaction has been accepted in WHILMA.
- Print out a *Dispensation Report (WHIP 0232)*, if desired, and file it in the participant's file.
- Give the appropriately-labeled bottle to the participant. Ask her if she prefers a non-child resistant cap. Ask her if she needs another *HRT Handbook*. Instruct her on how to take the pills. Remind her to bring the bottle back at the next visit. You may choose to affix a sticker to the bottle reminding the participant to return the bottle at her next clinic visit.

15.4.4 Selecting and Dispensing Open Label HRT Study Pills (Required)

The CC gynecologist may decide that a participant needs open label hormone medications. This decision may be made after scheduled visits or after an unscheduled visit for vaginal bleeding. Most often, open label hormones will be dispensed in response to results obtained from an endometrial aspiration, but they may also be dispensed in response to other treatment side effects (see *Section 5.4 - Managing Symptoms* for more details).

- Complete a *Form 54 - Change of Medications* each time you ask the participant to start, stop, or change the dosage of HRT study pills or open label medications. Record the date of the change, dosage of hormones and length of time prescribed. Algorithms and time frames are described in *Section 5.4 - Managing Symptoms.*
- Select and dispense open-label medication as described in *Vol. 5, Section 7.3.3.4 - Selecting Study Medications.*

- You must use WHILMA to select the appropriate open-label study pill bottle for the participant. Do not give a participant a bottle if it has not been selected by WHILMA. Dispense the open-label study pill bottle only after you have labeled the appropriate bottle with the participant's name and ID number. Do not give the bottle to the participant if there is any question whether the transaction has been accepted in WHILMA.
- Print out a *Dispensation Report* (*WHIP 0232*), if desired, and file it in the participant's file.
- Give the appropriately-labeled bottle to the participant. Ask her if she prefers a non-child resistant cap.
- Instruct the participant on how to take the open-label hormones.

  For example: "*Stop your normal WHI HRT pills. Take one of these pills daily*."
  or: "*Continue your normal WHI HRT pills. Take two of these pills daily*."

- Instruct the participant to bring the bottle back to the CC at her next CC visit (this will often be at unscheduled times for these participants).

15.4.5 Selecting and Dispensing CaD Study Pills (Required)

Calcium and Vitamin D study pills should be dispensed at the time of randomization to CaD using procedures similar to HRT study pill dispensing. See *Section 15.4.2 - Dispensing HRT Bottles at Screening Visit 3 (SV3) (Required)*. If the participant is eligible for CaD, randomize her to CaD, determine her preferred formulation, and select the appropriate CaD study pill bottle(s) to dispense as described in *Vol. 5, Section 7.3.3.4 - Selecting Study Medications.* Provide the participant with the *CaD Information Sheet (*see *Appendix - F.2.5 - You're an Important Part of the CaD Program*). Note: You will be dispensing two bottles for the first six-month period if the participant chooses the CaD chewable tablets or one bottle if she chooses the CaD swallowable pill. Dispense only a 6-month supply to the participant to ensure she is tolerant of the formulation. An annual supply may be dispensed once she has taken the same formulation for at least one year. Clinical Centers have the option of mailing the second 6-month supply (rather than conducting a visit), but should carefully assess the need for a participant to come in for a clinic visit.

CaD study pills are also dispensed at semi-annual and annual contacts using procedures similar to HRT study pills. See *Section 15.4.3 - Selecting and Dispensing HRT Study Pill Bottles at Semi-Annual and Annual Visits (Required)*. Participants should be offered the *CaD Information Sheet* and given study pill instructions each time CaD pills are dispensed. Note: You will be dispensing two bottles for each six-month period (4 bottles for a year) if the participant chooses the CaD chewable tablets or one bottle for each six-month period (2 bottles for a year) if she chooses the CaD swallowable pill. A 12-month dispensation can be done only at an annual visit contact.

15.4.6 Switching CaD Formulations

CaD formulations can be switched at any time, however, it is always best if you can wait until the next semi-annual (SA) or annual visit (AV) to minimize CC burden and preserve pill inventory. Remember, when a formulation is being switched, you need to collect the participant's old study pill bottle(s) and enter an actual weight or, if you are unable to collect the bottles, enter an estimated count, in WHILMA before dispensing the new formulation. Make every attempt to follow-up with the participant and collect the bottles if you did use an estimated count.

Switching formulations can be handled during an in-person clinic visit or by telephone. Carefully assess the need for the participant to come in for a clinic visit for taste/swallow tests and/or for adherence discussions.

If the participant comes into the CC for her routine clinic visit, collect her old CaD study pill bottles, assess adherence, and dispense new CaD study pills.

- If an estimated count was entered into WHILMA at the time she stopped taking her CaD study pills, replace it with the actual weight. Do not change the contact date when you enter the actual weight into WHILMA.

- If an estimated count was not done at the time she stopped taking her study pills, weigh the bottles and enter the weight into WHILMA. Use the date of the clinic visit as the contact date.

If switching formulations occurs at a non-routine clinic visit, collect her old CaD study pill bottles and assess adherence as you would for a routine clinic or contact and dispense new CaD study pills.

If the switch in formulations is made by telephone, ask the participant to stop taking her old study pills and to mail the old bottles back to the CC **as soon as she receives the new bottles**. CCs should provide participants with a self-addressed, stamped mailer. Mail the new study pill bottles to the participant immediately after the phone call. Ensure a CC staff person telephones the participants to confirm she received the new study pill bottle(s).

15.4.7 Selecting and Dispensing Study Pills for Remote Site Locations (Required)

A CC conducting follow-up visits at remote site locations must determine which procedures would best meet their specific needs. The options are to:

- Select the study pills in WHILMA in advance of a participant's scheduled clinic visit and dispense them to the participant at the clinic visit or

- Select the study pills in WHILMA after a participant's scheduled clinic visit and mail the study pills to the participant.

Either option will require the remote site to have the following supplies available: chewable tablets and swallowable pills for the CaD taste tests (to use before CaD randomization occurs), pill organizers, HRT Handbooks, consents for non-child resistant caps, non-child resistant caps, CaD consents, and the CaD Information Sheet.

15.4.7.1 Select the Study Pills before the Clinic Visit

Following are procedures that must be done at the main CC and the remote site:

Procedures at the Main CC:

- Use WHILMA to select the study pill bottle(s) for the participant's remote site clinic visit. To have the least effect on adherence, select the study pill bottle(s) either the evening before or the morning of the participant's scheduled clinic visit (at the remote site).

- Affix the participant's ID label to the study pill bottle(s), as usual.

- Carry the study pill bottle(s) to the remote site.

Procedures at the Remote Site:

- Store the study pill bottle(s) in a locked storage area at the remote site (i.e., do not store the study pill bottle(s) in the car).

- At the scheduled clinic visit, retrieve the previously dispensed study pill bottle(s) from the participant.

- Give the new study pill bottle(s) to the participant.

- Complete dispensation procedures in accordance with *Vol. 2, Section 15.4 - Study Pill Dispensing (Required)*.

- If the participant does not show for the scheduled clinic visit at the remote site, return the study pill bottle(s) to the main CC.

Procedures at the Main CC:

- Do an adherence collection for the participant's previously dispensed study pill bottle(s).
- If the participant did not show for her scheduled clinic visit, do an adherence collection for study pill bottle(s) not dispensed to the participant (indicating "0" adherence in WHILMA).
- If the participant did not show for her scheduled clinic visit and she is running out of study pills, from the main CC, select, label, and use overnight delivery service to mail the study pill bottle(s) to the participant.

15.4.7.2 Select the Study Pills after the Clinic Visit

Following are procedures that must be done at the remote site and main CC:

Procedures at the Remote Site:

- At the scheduled clinic visit, retrieve the previously dispensed study pill bottle(s) from the participant.
- Explain to the participant that her new study pill bottle(s) will be mailed (overnight delivery) from the main CC within 24 hours. Ask her to call the CC to report receipt of the study pill bottle(s).
- Complete dispensation procedures in accordance with *Vol. 2, Section 15.4 Study Pill Dispensing (Required)*.

Procedures at the Main CC:

- Do an adherence collection for the participant's previously dispensed study pill bottle(s).
- Complete dispensation procedures in accordance with *Vol. 2, Section 15.4 – Study Pill Dispensing (Required)*.
- Use overnight delivery service to mail the new study pill bottle(s) to the participant.

15.4.7.3 Strategies for Selecting and Dispensing Study Pills for Remote Site Locations

If the study pills are selected in WHILMA and labeled and the participant cancels the scheduled clinic visit, you must use your best judgment in this instance, depending on the situation (i.e., how soon can the participant reschedule the clinic visit). At the clinic's discretion:

- Mail the study pill bottle(s) to the participant or
- If the participant cannot reschedule within the week, do an adherence collection for the study pill bottles (indicating "0" adherence for the bottles). When the clinic visit is rescheduled, repeat the same procedures for dispensing at the remote site.

The decision to dispense open-label medications to a participant may be made during a scheduled remote site clinic visit or after an unscheduled remote site visit. Explain to the participant that the open-label medications will be mailed to her within the next 24 hours and she should begin taking them (as instructed) when she receives them. Select them in WHILMA and label the open-label medications at the main CC. Use overnight delivery service to mail them to the participant. If this is not the first time the participant is dispensed open-label medications, ask her to keep taking the open-label medications until empty and then start using the new open-label medications. Give her a postage-paid envelope to return the study pill bottle(s) to the main CC. Do an adherence collection for study pill bottle(s) not dispensed to a participant (indicating "0" adherence for the bottles).

If the participant wants to change CaD formulations, tell her that the changed formulation will be mailed from the main CC within 24 hours. Explain to the participant that she should begin taking them (as instructed) when she receives them. Select and label the new CaD formulation study bottle(s). Use overnight delivery service to mail them to the participant. Keep in mind that only a six month supply should be dispensed until the participant has been on the same formulation for one year. If the participant decides to change formulations, do an adherence collection for study pill bottles not dispensed to the participant (indicating "0" adherence for the bottles).

15.5 Selecting and Dispensing Problems (HRT/CaD) (Required)

A variety of situations or problems may arise when selecting and dispensing study tablet. With the exception of the HRT enrollment pill bottles, under no circumstances should you give a participant a bottle labeled with a bottle number other than the number assigned by WHILMA or the Clinical Coordinating Center (CCC). You are required to use the computer (WHILMA) to select study pills for *randomized* participants. If the computer is down, explain to the participant that you will mail her bottle to her when the computer is functioning again.

15.5.1 Abnormal Lab Results While On HRT Enrollment Pills

Participants may have abnormal or suspicious test results requiring follow-up while on the HRT enrollment pills. Abnormal tests results may include an abnormal pelvic exam, Pap smear, endometrial aspiration, transvaginal uterine ultrasound, clinical breast exam, or mammogram.

Follow the procedure below when you receive abnormal results:

- Ask the participant to stop taking her HRT enrollment pills until the abnormal results are resolved.
- Collect adherence information on the HRT enrollment bottle (or bottles) previously dispensed.
- Ask her to obtain appropriate follow-up evaluation and have results sent to the CC.
- Record the results of the follow-up evaluation on the appropriate form.
- If the participant is eligible to continue screening, start a second HRT enrollment period (see *Section 15.4.1.3 - Repeat HRT Enrollment Period*). Dispense a new bottle to the participant, indicating in WHILMA that the bottle is for a second enrollment period.

15.5.2 Bottle is Lost or Damaged Before You Dispense It (Required)

If the bottle selected for dispensing is lost or damaged and you cannot give it to the participant:

- Disable the bottle using the appropriate WHILMA option (see *Vol. 5, Section 7.3.3.1 - Managing Medication Inventory*).
- Re-run the selection function to select the next bottle.
- Dispense the selected bottle to the participant.
- Return the damaged HRT or CaD study pill bottle to McKesson, indicating when you found the damaged bottles. Returning the damaged bottle will help McKesson assess the type of damage problems you are finding and provide feedback to the drug manufacturer.

If you later find a bottle that you reported lost, do not dispense it to the participant. Return the bottle (which should already be disabled) to McKesson as described above.

15.5.3 Participant Has a Lost or Damaged Bottle (Required)

If a participant loses or damages a bottle you dispensed to her, conduct an adherence collection (estimated count or actual weight) for that bottle as a soon as she reports the loss or damage and dispense another bottle to her. Use the same procedure described under selecting and dispensing at the semi-annual or annual visits [see *Section 15.4.3 - Selecting and Dispensing HRT Study Pill Bottles at Semi-Annual and Annual visits (Required)* above] to select a new bottle number.

- Mail a new bottle in a padded envelope.
- If the previous bottle was damaged rather than lost, instruct the participant to return it immediately to the CC.
- Supply a self-addressed stamped mailer for mailing back the damaged bottle.

- Remind the participant that all bottles should be returned at the next visit.

If this occurs a second time for a participant, investigate the problem and take appropriate steps to resolve it.

15.5.4 Participant's Supply Runs Out (Required)

15.5.4.1 HRT Enrollment Pills

Run the *Enrollment Medication Reminder Phone Call Report (WHIP 0227)* in WHILMA to identify participants who will run out of enrollment pills during a specified time period. Select and dispense a second bottle as needed (see *Vol. 5 - Data System, Section 9 - Queries and Reports* for instructions on running reports). WHILMA calculates adherence from the weight of each bottle, the date of dispensation, and the date of adherence collection for that bottle.

15.5.4.2 Study Pills (HRT, CaD)

If a participant calls to ask for additional pills because her last bottle is empty:

1. Determine the date of the next regularly scheduled visit.
2. If the next visit is less than one week away, do not mail a new bottle.

   If the participant seems concerned, explain that by the time the bottle arrived, it would almost be time for the visit. Also, because of the cost and the potential for losing or being delayed in the mail, it is better to dispense the bottle in person.
3. If the next visit is more than a week away, determine why the participant has a study pill shortage. Possible explanations are:
   - lost or damaged bottle or pills
   - missing visit or visit done outside window
   - sharing of pills
   - improper dosings (over-medicating)
   - inadequate supply originally
4. If indicated, mail the appropriate bottle and have her return her old bottle(s) by return mail.

Do not allow participants to use the pill-mailing option as a means of avoiding a regular visit, unless absolutely necessary for retention (see *Section 16.4.1 - Strategies for Avoiding Missed Contacts*).

If the participant is over-medicating, it is important to know this and advise her against this. Inform your Clinic Practitioner (CP) and ask for further assistance in deciding whether to mail an additional bottle.

If the participant is sharing pills with someone else, it is unlikely that she will volunteer this information. If she does, strongly discourage any further sharing. Mail an additional bottle as described above after the participant has agreed not to share.

15.5.5 No Bottles Available (Required)

If all of the bottles identified by WHILMA for dispensing to a participant are missing, contact the CCC Data Coordinator immediately. If WHILMA displays an “insufficient inventory” message when you attempt to select a study pill bottle, notify McKesson immediately by phone, eMAIL, or fax to order additional study pill supplies. Tell the participant that you will be mailing the bottle to her. Also review your ordering procedures with McKesson to determine why you did not have an adequate supply of bottles in stock. Review the *Drug Inventory* report (*WHIP 0032*) from WHILMA at least quarterly and use it to monitor your study pill supply.

15.5.6 Participant Drops Out (Required)

When a participant is told or asks to discontinue study pills (or informs the CC that she is dropping out), collect her study pill bottle(s) and adherence data immediately and complete the appropriate WHI forms (which may include *Form 54 - Change of Medications* and/or *Form 7 - Participant Status*). Refer to *Section 17 - Retention* for additional information on participant status.

15.5.7 Transferred Participants (Required)

During the course of the study, participants randomized at one CC may transfer to another CC. Select and dispense study pill bottles to participants transferred to your clinic as you do for routine participants. See *Section 17.5 - Transfer of Participants Between Clinical Centers* for procedures on transferring and receiving participants.

15.5.8 Reactivated Participants (Required)

Select and dispense study pills to reactivated participants as you do to active participants. When you schedule a reactivation visit for a participant, check the participant file to be sure there is a label for the bottle. See *Section 17.4.5 - Reactivation of Participants with Changes in Participation Status.*

15.6 Study Pill Adherence Monitoring (Required)

The CC must accurately monitor the participant's adherence to the HRT and/or CaD interventions. Non-adherence to the daily pill regimen may dilute any true difference between the intervention arms.

The CC assesses the participant's adherence to taking study pills by weighing returned study pills (HRT) or study pill bottles (CaD) or by self-report of the number of estimated pills remaining in the bottle if bottles are not returned. However, CCs should encourage the participant to return the old bottle(s) by mail using a prepaid mailer supplied by the CC. Actual weight is preferred over estimates.

If study pills are dispensed to a participant on a semi-annual basis (every 6 months), adherence data should be entered in WHILMA for that participant every 6 months. If study pills are dispensed to a participant on an annual basis (every 12 months), adherence data should be entered in WHILMA for that participant every 12 months.

Clinical Centers that dispense an annual supply at annual visits will still be expected to assess adherence at semi-annual contacts. Do not enter this estimate into WHILMA. Request all bottles at the next annual visit.

From the adherence data, the CCC will calculate pill consumption rates over time for each participant. Mean study pill consumption rates are reviewed semi-annually by the WHI Council, Data and Safety Monitoring Board, and NIH.

15.6.1 Purpose

The purpose of monitoring study pill adherence is to:

- establish eligibility at SV3 (for HRT participants)
- determine participant's actual pill consumption rate
- distinguish participants with good adherence from participants with poor adherence when implementing focused programs to boost adherence
- determine reasons why participants don't take their study pills
- determine how participants make up for missed pills (if at all)

15.6.2 Adherence Assessment

Adherence is determined by weighing the returned study pills (HRT) or study pill bottle (CaD). The procedure is similar for all types of clinic contacts. *Figure 15.5 - Study Pill Adherence Assessment For Follow-Up Procedures* provides a flow chart for making decisions about appropriate adherence assessment procedures.

15.6.2.1 Approach to Participant (Required)

Use the following procedures in assessing the participant's study pill adherence. If participants ask why they must return unused pills and empty bottles, you may tell them:

- to perform quality assurance checks
- to check for deterioration of the unused pills
- to comply with FDA requirements for returning investigational drugs to the study center

To ensure useful adherence information is obtained:

- do not tell participants that you measure pill adherence by weighing returned study pills or study pill bottles
- do not weigh the study pills or study pill bottles in front of the participant
- do not confront participants with pill weight or count information as the basis for admonishing or encouraging them towards better adherence
- assume that the participants take the pills as prescribed unless they volunteer or acknowledge on self-report that they are not taking them

If a participant asks if you are weighing or counting the pills, do not deny it. You might simply say "I have noticed that there seem to be more pills left in the bottle than I expected," and then proceed to explore the reasons for non-adherence. If appropriate, you might say, "It appears that you are taking most of your pills as you should."

When dispensing study pill bottles, explain to the participant that you want her to bring in any unused pills in the original bottle, pill organizers containing pills, and any empty study pill bottles at the next visit. You may affix a sticker to the bottle as a reminder for the participant to return her study pill bottle at each clinic visit. A reminder postcard will also help the participant remember to bring in all study pill bottles she has.

15.6.2.2 Weighing Procedures (Required)

The weight of the returned HRT or open label study pills, and CaD study pills and bottles, rather than pill count, will be used to calculate adherence. (Study pill bottles are not weighed before they are dispensed). If the bottles are not returned, estimated pill counts are used to calculate adherence. Do not be concerned about weight differences between study pill bottles. WHILMA will calculate adherence appropriately. Any perceived differences between the weights of the study pill bottles should not be discussed with participants.

1. Equipment/Supplies

- OHAUS Portable Advanced Electronic Balance (Model CT1200)
- Two calibration masses: 1000 g weight and 500 g weight
- OHAUS Instruction Manual: Read the accompanying manual before you use the scale
- Pill scoop

Service Information:

If the Troubleshooting section does not resolve or describe your problem, contact an authorized OHAUS Service Agent (1-800-526-0659). In New Jersey, call (201) 377-9000. Contact the CCC to request a loaner.

a. Initial Scale Set-Up

Selection of Unit Weight (refer to pages 21 and 22 of the OHAUS Instruction Manual): the scales are set up at the factory to read in "gram" units. **Do not change this setting**.

Selection of Platform: remove the cup weighing container from the scale and use the accompanying platform attachment instead.

b. Daily Set-Up

Scale Set-Up: with nothing on the platform, press the "On Tare" button. Allow at least 5 minutes for the balance to temperature stabilize before using.

Calibration: the OHAUS balance is calibrated in two ways before shipment: for Span and Linearity. Span calibration resets the balance weighing range using two weight values: zero, and a weight value at or near the balance's capacity. Linearity calibration is performed before shipment and should not need to be repeated. If determined that linearity calibration is needed, follow the procedures given in the OHAUS Instruction Manual (page 18).

Calibrate the scale each day before it is used following the procedure below. Span calibration should also be done each time you move the scale and after rough handling.

Span Calibration: (refer to page 17 of the OHAUS Instruction Manual):

- Remove all weight from the platform. Have the 1000 g weight available.
- Press and hold "On Tare button" until CAL is displayed, then release it. The balance will display SPAN.
- Press The "On Tare" button again. When released, "C 0 g" will be displayed. This indicated that no weight should be on the platform.
- Press "On Tare" for the third time.
- When it is released, the display window will show "-C-" briefly, then "C" followed by the value of the calibration mass (1000 g) to put on the platform. DO NOT disturb the balance or place anything on the platform when "-C-" is displayed. The balance is waiting for a stable weight reading and disturbances will result in improper calibration.
- Place the 1000 g weight on the platform, then press the "On-Tare" button.
- The display window will show "-C-" while the balance re-calibrates itself. DO NOT REMOVE the 1000 g weight at this point. When the balance returns to the normal weighing mode (the Unit Indicator will appear in the display window), span calibration is completed. Remove the 1000 g mass from the platform and store.
- To exit the calibration mode, press "Off mode" until END is displayed. Press "On Tare" to return the balance to normal weighting operations.
- Note: the scale is extremely sensitive and will drift with any additional motion in the area. Take the reading as soon as the value seems to have stabilized. Drift will also occur if the mass is left on the platform for a longer period of time.

2. Weighing Study Pills

The procedures for weighing returned HRT and CaD study pills are different in one way, in that you

- weigh HRT pills **without** the bottle and
- weigh CaD pills **with** the bottle and cap.

The actual weighing procedures cannot be monitored by WHILMA, therefore WHILMA will not notify you if you use incorrect weighing procedures. HRT adherence assessed on weights that include the HRT bottle will be inappropriately low. To remind staff of the weighing procedures, post the Study Pill Weighing Procedures (see *Figure 15.4*) near the scale.

a. Weighing HRT Study Pills

Weigh all returned **HRT or open label study pills (without the bottles)**, including HRT study pills from unopened bottles, and from pill organizers.

- With an empty scale platform, press "On Tare".
- Place the empty pill scoop on the platform. Its weight will be displayed.
- Press "On Tare" again. A zero will be displayed.
- Pour the study pills into the scoop and read the weight. The weight displayed will be that of the study pills alone.
- Key-enter the weight of the pills into WHILMA and record the adherence rate the appropriate line of question 5, *Form 10 - HRT Management and Safety Interview*.
- If you have multiple HRT pill weights to assess, empty the scoop, add the next study pills, and repeat step #5. (The tared weight will remain in memory until "On Tare" is pressed again.)
- To change to weighing CaD bottles, first clear the memory by pushing "On Tare" or turn the scale off. Then follow the procedures for weighing CaD bottles below.

Reference: OHAUS Scale Instruction Manual, page 12.

a. Weighing CaD Bottles

- Weigh the swallowable CaD pill **bottles** (leaving the pills in the bottle) and the chewable CaD tablet **bottles** using the same procedure. WHILMA knows which formulation is being collected by the bottle ID.
- Weigh all returned CaD study pill **bottles** returned by the participant, including CaD study pills from unopened bottles, and from pill organizers. **Weigh CaD bottles** WITH the original child-resistant caps. Keep an extra CaD child-resistant outer shell cap near the scale in case the original outer cap has been removed. If the child-resistant cap was replaced with a non-child resistant cap or the outer shell cap was removed, place the outer shell cap on the scale when the bottle is weighed. (You don't need to attach the shell to the bottle cap; instead lay the shell on the scale platform.)
- Wait until the scale indicator appears before reading the displayed weight. (This should take no more than 5 seconds.) When the indicator appears, the reading is stable. Note: The scale is extremely sensitive and will drift with any additional motion in the area. Take the reading as soon as the value seems to have stabilized. Drift will also occur if the mass is left on the platform for a longer period of time.
- If weighing multiple bottles, wait for the scale to read "0 g" before putting another bottle on the scale.

3. Enter Adherence Data (HRT/CaD)

Enter the adherence information into WHILMA as described in *Vol. 5, Section 7.3.3.5 - Medication Adherence.* If you are not able to enter the weight directly, write the date and the weight directly on the bottle for future reference.

4. Estimated Pill Count When Bottle is Not Available (HRT/CaD)

CCs need to make every effort to obtain bottles from participants. When this is not possible an estimated count is an acceptable alternative. Obtain the adherence data for each bottle not returned by asking the participant how many pills remain in each unreturned bottle. If the participant does not know the number remaining, ask her to estimate the number remaining (e.g., is the bottle 3/4, 1/2, or 1/4 full). (See *Section 15.6.2.6 - Bottles Not Returned (Required)* for more details.)

Enter the estimated count into WHILMA as described in *Vol. 5 - Data System, Section 7.3.3.5 - Medication Adherence Collection* and in the addendum to the v.35 upgrade notes. If you later receive the bottle on which you estimated the count, weigh the bottle or pills, delete the estimated count, and enter the weight into WHILMA.

Figure 0.4

STUDY PILL WEIGHING PROCEDURE

HRT - Weigh pills **without** the bottle

1. With an empty scale platform, press "On Tare".
2. Place the empty pill scoop on the platform. Its weight will be displayed.
3. Press "On Tare" again. A zero will be displayed.
4. Pour the study pills out of the bottle into the scoop and read the weight. The weight displayed will be that of the study pills alone.
5. Key-enter the weight of the pills into WHILMA and record the adherence rate *Form 10 -HRT Management and Safety Interview.*
6. If you have multiple HRT pill weights to assess, empty the scoop, add the next study pills, and repeat step #5. (The tared weight will remain in memory until "On Tare" is pressed again.)

CaD - Weigh pills **with** bottle and cap.

1. Clear the memory by pushing "On Tare" or turn the scale off then on again. A zero will be displayed.
2. Place the bottle with the cap on the scale. If the cap is a non-child resistant cap, see procedures in *Vol. 2, Section 15.6.2.2 - b) Weighing CaD Bottles.*
3. Key-enter the weight into WHILMA and record the adherence rate on *Form 17 - CaD Management and Safety.*
4. If you have multiple CaD bottle weights to assess, repeat step 2.

Reference: *OHAUS Scale Instruction Manual*, page 12.

15.6.2.3 HRT Enrollment Adherence (Required)

When assessing HRT enrollment adherence, use one of the following dates as the encounter date in WHILMA:

- If the participant brings the bottle to the visit, use the date the CC collects the HRT enrollment bottle from the participant.
- If the participant loses the bottle and/or pills, use the date the participant contacts the CC to report that she has lost the HRT enrollment bottle and/or pills in the bottle.
- If the participant runs out of pills, use the date the participant contacts the CC to report that she ran out of HRT enrollment pills.

Do not use the date the participant says she lost the bottle or ran out of pills. Use the date she contacts the CC.

If a participant is ineligible due to the HRT enrollment adherence criterion, you can repeat the enrollment one time only. See *Section 15.4.3 - Repeat HRT Enrollment Period*.

To assess and document enrollment adherence:

- Determine adherence by weighing the enrollment bottle (refer to weighing procedure above).
- Enter the bottle weight into WHILMA as described in *Vol. 5 - Data System, Section 7.3.3.5 - Medication Adherence Collection* (released initially in the addendum to the WHILMA v.35 upgrade notes).
- The database will determine the participant's adherence eligibility based on the number of days between dispensing and adherence collection, and the number of pills returned as calculated from the bottle weight.
- Empty the weighed pills into the HRT discard container. See *Section 15.3.4 - Returning Study Pills to Mckesson (Required)*.

15.6.2.4 HRT and CaD Semi-Annual and Annual Follow-Up Contacts (Required)

In general, the sooner the study pill bottles are collected from the participants, the more likely the data will be accurate.

1. When the participant returns used bottles at a CC visit, do the following:

   - Take the returned bottles and the participant's file with you when you leave to get the new bottles of study pills for the participant. If the participant asks you why you are taking the bottles with you, tell her that it is to cross-check the bottle ID and name on the old and new bottles. See also *Section 15.6.2.1 - Approach to the Participant*.
   - Verify that the bottle ID number on the returned bottles matches the bottle ID number from the file.
   - Follow the procedures described in *Section 15.6.2.2 - Bottle Weighing Procedure To Weigh Pills and/or Bottles.*
   - Enter the weight into WHILMA as described in *Vol. 5, Section 7.3.3.5 - Medication Adherence Collection.*
   - Empty the weighed pills into the HRT and/or CaD discard container. See *Section 15.3.4 - Returning Study Pills to McKesson*.
   - When assessing multiple bottles the participant returned at the same time, be careful to record the correct weight for the corresponding bottle number.

2. When the participant is dispensed a 6-month supply at her AV1 and her next contact (SA2) is conducted by phone, do the following:

   - During the phone contact, ask the participant to estimate the number of study pills remaining in her study pill bottle(s) and record her estimate on *Form 10 - HRT Management and Safety Interview* or *Form 17 CaD Management and Safety Interview*.

   - Create an adherence collection encounter (*Task 951* in WHILMA). The contact date of *Task 951* should be the date of the phone contact where the estimate was obtained from the participant. Enter the estimated count from *Form 10 - HRT Management and Safety Interview* or *Form 17 - CaD Management and Safety Interview*.

   - Tell the participant you will mail her next supply of study pills along with a pre-paid mailer to return the study pill bottles she currently has. Ask her to continue to take study pills out of the current study pill bottle until she receives the new supply. Tell her to stop taking study pills out of the old study pill bottle and start taking study pills out of the new study pill bottle when she receives the new supply. (Note: Use of prepaid mailers is strongly recommended, but not required.)

   - Ask her to mail the old study pill bottles back to the CC at her earliest convenience. Suggest she mark an "X" through the label of the old study pill bottle.

   - When you receive the old study pill bottles at the CC, weigh them following the appropriate procedures for CaD and HRT.

   - Go into the *Task 951* created for the corresponding bottle(s) on the date of the phone contact and delete the estimated count. Enter the actual weight of the pills (HRT) or bottles (CaD). Do not change the contact date when you enter the actual weight into WHILMA.

   If the participant keeps the bottles until her next clinic visit, ask the participant to put an "X" through the label of the old study pill bottle(s) to ensure she does not get the old and new study pill bottle(s) mixed up.

   If the study pill bottles are not collected, obtain an estimated count to enter into WHILMA. Take any appropriate steps to collect the study pill bottle(s) from the participant (e.g., give) her a pre-paid mailer to mail the study pill bottle(s) back to the CC. If this is not feasible, ask her to return the study pill bottles at the next contact.

15.6.2.5 HRT and CaD Bottles Returned by Mail (Required)

When assessing adherence on bottles returned by mail, use the following procedures (see *Figure 15.5 - Study Pill Adherence Assessment (For Follow-Up Contact)*):

- If the participant returns used bottles by mail, follow the steps for bottles returned at visits to weigh the study pills and/or bottle.
- If the participant reports to the CC by phone before mailing the bottle, use the date of the phone call as the adherence date.
- If she mails the bottle without having called, use the date the bottle is received by the CC.
- If a pill estimate was previously done on the returned bottle, delete the previously entered estimated count from the database and key-enter the weight.

15.6.2.6 HRT and CaD Bottles Not Returned (Required)

If a participant does not bring the used study bottle to SV3 or the routine follow-up visits (see *Figure 15.5 - Study Pill Adherence Assessment (For Follow-up Contact)*, encourage her to mail the bottles and remaining pills back to the CC and send her a prepaid mailer. At the contact, use the following procedures:

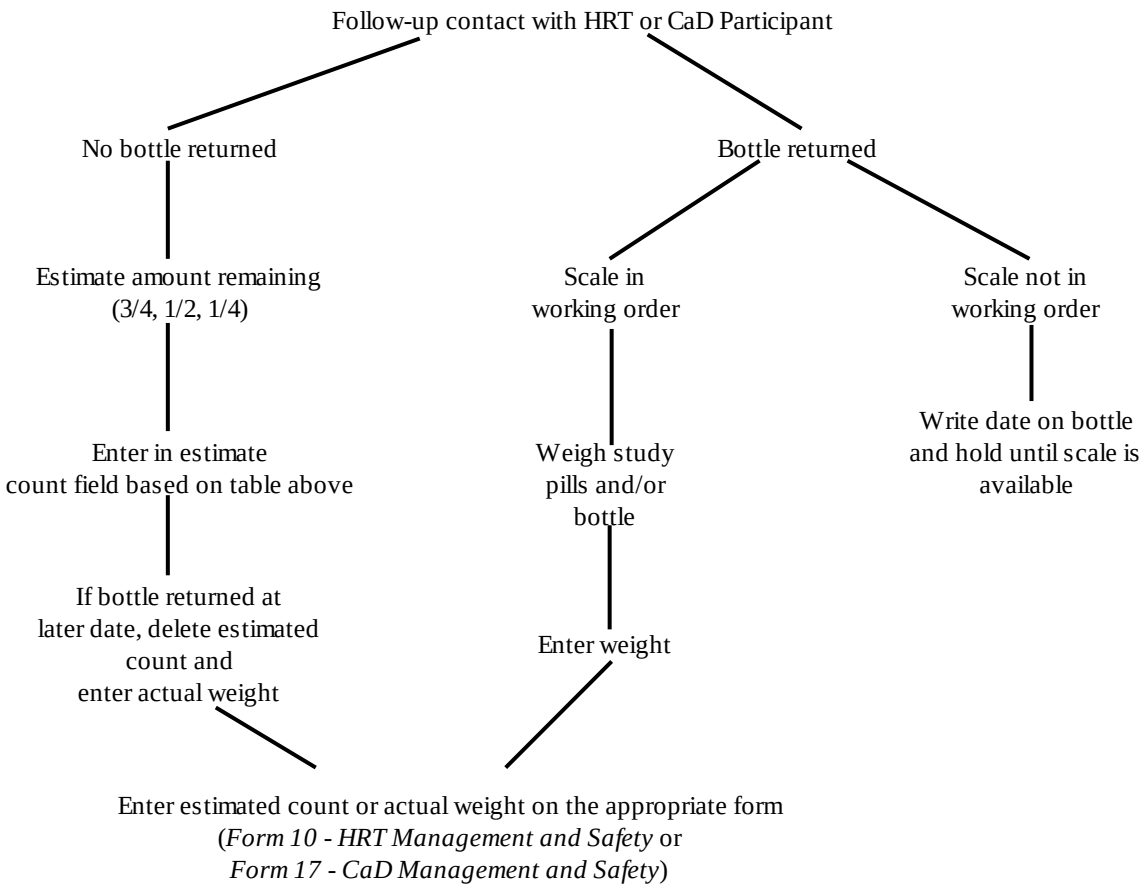
- Determine the last bottle number dispensed to the participant by reviewing the *Dispensations Report (WHIP 0232)*.

  Obtain the adherence data for each unreturned bottle by asking the participant how many pills remained in each unreturned bottle. If the participant does not know the number of pills remaining, ask the participant to estimate the number remaining (e.g., is the bottle 3/4, 1/2, or 1/4 full). Use interviewing techniques (see *Section 2 - Clinical Center Guidelines*) to get the participant to give you an estimate. Note that a bottle with the full complement of study pills may not be filled to the top with pills. Ideally, pill estimates should account for this fact. Use the following table as a guideline for converting their responses:

Response	# of HRT Pills Remaining	# of HRT Open Label Pills Remaining	# of HRT Enrollment Pills Remaining	# of CaD Chewable Tablets Remaining	# CaD Swallowable Pills Remaining
"Full" bottles	215	100	50	215	430
"Half full"	110	50	25	110	215
"Almost empty"	25	10	5	25	25

- Enter the estimated count into WHILMA described in *Vol. 5, Section 7.3.3.5 - Medication Adherence Collection*.
- Tell the participant not to take any more study pills from the used bottles.
- Provide the participant with a self-addressed stamped mailer and ask her to mail the used bottles to the CC, or ask the participant to return the bottles at the next visit. Collect actual adherence information when these bottles are received.
- If a participant reports losing a bottle, conduct an adherence collection immediately. Have her estimate the number of pills left in the bottle when she lost it.

Figure 0.5
Study Pill Adherence Assessment (For Follow-Up Contact)



15.7 Study Pill Problems

15.7.1 Overdose

The CCC provides each CC and the nation-wide Poisindex with a study-wide statement regarding study pills used in the HRT and CaD trials. The statement includes the chemical names and dosages of all study pills used along with the possible number dispensed. Attached to the statements are the Poisindex listing for estrogens and progestins or calcium and vitamin D, as well as a list of the CCs, their phone numbers, addresses and Principal Investigators (PI). Clinical Centers may copy and distribute this to their local poison control, emergency rooms in the area, and any other agency that may be involved in an overdose situation.

In general, overdose of hormones has not been found to result in life-threatening situations and conservative treatment has been sufficient. Symptoms usually consist of nausea and/or vomiting.

Overdose of calcium and vitamin D supplements may rarely result in a condition known as hypercalcemia. Participants may describe deep bone or flank pain, loss of appetite, nausea, vomiting, thirst, constipation, a tendency to trip or to drop things, changes in heart rhythm or lethargy. Psychosis is also a manifestation of hypercalcemia. Vitamin D overdose symptoms are identical to those of calcium overdose.

Use the guidelines below to manage all calls related to study pill overdose.

15.7.1.1 Treatment

Women's Health Initiative CC staff should not provide or recommend treatment for WHI study pill overdose. Treatment of an actual or suspected overdose should be provided by one of the following resources: a local Poison Control Center, a local **emergency** center, or the participant's primary physician. Each CC should decide to which resource these calls will be referred and then create an internal procedure for such referral. Treatment guidelines should be available in your CC's Internal Manual for reference by staff or these community resources.

15.7.1.2 Unblinding

Standard treatment for overdose of HRT or CaD study pills may be initiated per the Poisindex recommendations with out unblinding the participant's study arm. There may be extreme circumstances, however, where unblinding is deemed necessary. In these cases, the CC consulting gynecologist CC medical director, or PI should be notified and the unblinding procedure initiated (see *Section 5.6 - Unblinding* for HRT and *Section 7.3.4 - Unblinding* for CaD).

15.7.1.3 Managing Overdose Calls

Use the following procedures to manage a call to the CC regarding study pill overdose:

1. Inform the caller that you need some information and that you will refer the call to the local Poison Control Center, the local emergency center, or the participant's primary physician (depending on your CC's policy).
2. Document the following information:
    - name and telephone number of caller
    - name of WHI participant
    - name and age of person (if not the participant) who consumed the study medication pills
    - approximate number of pills consumed
    - WHI bottle number

1. Refer the call to the local Poison Control Center, local emergency center, or the participant's primary physician (depending on your CC's policy).
2. If study pill unblinding is deemed necessary, ask the local Poison Control Center, the local emergency center, or the participant's primary physician to call the CC consulting gynecologist, medical director, or PI.
3. Document the incident in the participant's file.
4. Present the overdose case at the next CC staff meeting. This will be useful in reviewing and revising appropriate CC policies.

Note: If you refer overdose calls to the participant's primary physician, you may need to provide WHI treatment protocol guidelines to the primary physician.

15.7.2 Serious Adverse Experiences (SAEs)

Serious Adverse Experiences (SAEs) are reported and monitored through WHI outcomes processing and analysis. The Food and Drug Administration (FDA) has approved this strategy for the WHI HRT and CaD trials. Clinical Centers should consult with their local IRBs to determine if additional reporting and monitoring is required locally.

15.8 Managing Adherence

Adherence to study pills is an important part of the WHI study design and critical for testing the study hypothesis. Assess for and act on adherence problems at all participant contacts. See *Section 17.2 - CC Activities for Retention Challenges* for retention activities related to adherence, reasons for poor adherence, and activities to ensure full adherence.

15.8.1 Intensive Adherence Program (Required)

The Intensive Adherence Program is a required series of special participant contacts without data collection, aimed at improving poor adherence and dealing with pill adherence problems. Intensive Adherence Program contacts are made with participants who report low adherence levels or because of CC staff referral for adherence problems. The number, frequency, and content of the contacts vary according to participant need and CC staff discretion. Refer to *Section 17.2.5. - Intensive Adherence Program* for more detail on this important adherence management strategy.

Table 0.2
WHI Placebo Ingredients (PERT Placebo)

Core Ingredients:	Input/Tablet	Representative Batch Formula 100,000 Tablets
Polyethylene Glycol, 8,000, NF	28.8 mg	2.88 kg
Lactose, NF	86.4 mg	8.64 kg
Magnesium Stearate, NF	0.60 mg	0.06 kg
Talc, USP	4.20 mg	0.42 kg
Theoretical Core Weight - 120 mg		
Coating Ingredients:[A]		
Seal Coat		
Polyethylene Glycol Type 20,000	0.30 mg	0.03 kg
Alcohol, Denatured, 23A[B]	—	0.024 kg
Glyceryl Monooleate	0.150 mg	0.015 kg
Shellac Solution, White, 4# Cut[C]	5.62 mg	0.56 kg
Calcium Sulfate, NF Anhydrous	10.7 mg	1.07 kg
Inert Filler Coat		
Microcrystalline Cellulose, NF	7.32 mg	0.73 kg
Sucrose, NF	97.6 mg	9.76 kg
Titanium Dioxide, USP	0.10 mg	0.01 kg
Purified Water, USP[B]	—	3.80 kg
Placebo Filler Coat		
Povidone, USP	1.56 mg	0.16 kg
Purified Water, USP[B]	—	5.61 kg
Sucrose, NF	102 mg	10.2 kg
Color		
Purified Water, USP[B]	—	0.94 kg
Sucrose, NF	18.9 mg	1.89 kg
Titanium Dioxide, USP	0.45 mg	0.045 kg
Polish		
Carnauba Wax, NF	0.16 mg	0.016 kg
Mineral Spirits, Odorless[B]	—	0.033 kg

[A] These quantities per tablet represent theoretical amounts of coating materials applied. The actual amounts may vary depending on coating efficiency, tablet characteristics and processing conditions.

[B] Removed during processing.

[C] This represents the amount of solution at a theoretical solids content of 34.8% w/w.

Table 0.3
WHI Placebo Ingredients (ERT Placebo)

Core Ingredients:	Input/Tablet	Representative Batch Formula 100,000 Tablets
Color		
Purified Water, USP[A]	—	0.97 kg
Sucrose, NF	24.7 mg	2.47 kg
Titanium Dioxide, USP	1.72 mg	0.17 kg
Polish		
Carnauba Wax, NF	0.12 mg	0.012 kg
Mineral Spirits, Odorless[A]	—	0.025 kg

Table 0.4
WHI Chewable CaD Ingredients

Chewable Active	Chewable Placebo
Calcium Carbonate, USP	Sugar, Compressible, NF
Starch, Modified Corn, NF	Starch, Modified Corn, NF
Confectioners Sugar, NF	
Talc, USP	Contrasweet Powder (MM32)
Light Mineral Oil, NF	Peppermint Powder, 20% Spray Dried
Sodium Hexametaphosphate, FCC	Magnesium Stearate, NF
Peppermint Powder, 20% Spray Dried	
Vitamin D3, Dry Type, 100 CWS	

[A] Removed during processing.

Table 0.5
WHI Swallowable CaD Ingredients

Swallowable CaD Active	Swallowable CaD Placebo
Oyster Shell Granulation	Lactose Anydrous NF
Corn Starch NF	Microcrystalline Cellulose NF
Calcium Stearate NF	Magnesium Stearate NF
Talc USP	FD&C Blue #1 Aluminum Lake
Sodium Starch Glycolate NF	D&C Red #30 Talc Lake
Vitamin D3	FD&C Yellow #6 Aluminum Lake
Coating Solution Solids	Coating Solution Solids
Carnauba Wax NF	Carnauba Wax NF

Section 15
Medications (Study Pills)

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