7. Central Laboratory Procedures

Introduction

The Core Laboratory for Clinical Studies (CLCS) of Washington University Medical School will serve as the central laboratory for OMNI Heart. The NHLBI will serve as the repository for the storage specimens. Specimens will also be sent to the Sacks Lab and to local labs from each site. This manual contains the information needed to collect, process, and ship specimens to the laboratories for analysis and the repository for storage. Please review the manual before the beginning of the study and contact the central laboratory or the repository if you have any questions or require additional information.

Contacts at CLCS

Customer Service (314) 362-3522
Email: CLCS@im.wustl.edu

Laboratory Fax Number (314) 362-4782
Website: http:/clcs.wustl.edu

Laboratory Director
Thomas Cole, Ph.D.

Laboratory Manager
Connie Ferguson, MBA, M.T. (ASCP)

Clinical Studies Coordinator
Judi Jones BS, MT

Information Systems Supervisor
Dave Gibson

Technical Supervisor
Caswalyn Landry MS, C-MT (ASCP)

U.S. Mail Address:

Core Laboratory for Clinical Studies
Washington University School of Medicine
660 S. Euclid Ave., Box 8046
St. Louis, MO 63110

Shipping Address: (Federal Express)

Core Laboratory for Clinical Studies
Washington University School of Medicine
4940 Parkview Place
St. Louis, MO 63110

Contacts at NHLBI

Shipments to the NHLBI central storage facility will be coordinated through:

Misti Dowell
BBI Biotech Research Laboratories
NHLBI Repository
217 Perry Parkway
Gaithersburg, MD 20877
Voice (301)208-8100 ext 107
Fax (301)208-8829
e-mail nhlbi@bbii.com

Shipping address: (UPS & FedEx): Contact Misti Dowell before shipping.

Study Supplies

The following will be provided before screening begins:

- Blood collection tubes
- Labels and vials for specimen aliquots
- Shipping and storage boxes for specimens
- Urine collection hats and jugs
- Disposable transfer pipettes

The following will be provided as requested for specimen shipments

- Shipping containers and supplies
- Pre-addressed Federal Express Airbills

The CLCS will distribute specimen collection kits, supplies and shipping containers directly to each center as requested. Request supplies by submitting a Supply Request From to the CLCS. See Appendix B for a copy of the Supply Request Form.
Contact the CLCS at least 2 weeks before your Lab Supplies are needed.
The provided supplies must be used only for this study. If a large number of redraws or abnormal situations occur, inform the CLCS of the need for replacement supplies. Each center will be responsible for maintaining an adequate inventory of supplies.

The following are found on the OMNI Heart website:

- Central Laboratory Operations Manual (Lab Procedures, Chapter 7)

- Central Lab Collection Form- 24-Hour Urine (Form #30)
- Central Lab Collection Form - Fasting Blood (Form #31)
- Central Lab Shipping Log - Urine (Form #38)
- Central Lab Shipping Log - Blood (Form #39)

The following must be available at each clinical center:

- Standard refrigerated clinical centrifuge
- Ultra-low temperature freezer -70°C or colder, (i.e., ultra low REVCO or equivalent). All blood specimens must be stored at -70°C. If necessary, urine specimens may be stored in a non-cycling -20°C freezer, for up to 30 days before shipping.
- Dry Ice for shipping
- Federal Express pick-up or drop-off service
- Racks for tubes
- Phlebotomy supplies
- Indelible markers for labels
- Biological waste bags
- 2 L graduated cylinder for measuring urine volume
- Deionized/Distilled Water for rinsing the cylinder

Preparing for the Visit:

Materials Needed

- Visit-specific kits (see description below)
- Visit and participant specific labels

Note: Request preprinted labels for each participant by e-mailing the ID to the CLCS at least one week prior to the SV3 visit. The format for the participant ID is ID# (space) Accrostic. Use this format to request labels and to complete Forms 38 and 39.
Labels will be printed and sent to the site via Federal Express. A complete set of labels to be used throughout the study will be provided.

Description of Visit Kits used for Blood Draws

A single kit of blood collection supplies will be used for all visits including:
SV3, PI-4, PI-6, PII-4, PII-6, PIII-4, and PIII-6.

Plasma Kit contains:

3 x 10 mL EDTA Vacutainer tubes (purple top)
1 x 30 mL plastic pooling vial (purple cap)
10 x 2 mL plastic freezing vials (purple caps)

Note: 1 x 2 mL plastic freezing vials (plain top for buffy coat) required at Visit PI-4 only.

Serum Kit contains:

3 x 10 mL SST Vacutainer tubes (red/black top)
1 x 30 mL pooling vial (red cap)
10 x 2 mL plastic freezing vials (red caps)

Description of Visit Kits used for Urine Collection

Urine collection hats and jugs will be provided in bulk for distribution prior to visits SV3, PI-6, PII-6, and PIII-6. Labels are included in preprinted label set.

Urine Supplies

24-hour urine collection jug
Labels for jugs
6 x 8 mL plastic freezing vials (yellow caps)

Additional Supplies

Transfer pipettes (bulk supplies)
Shipping supplies (airbills, coolers, boxes, Dry Ice stickers, etc.)

Prepare the Labels

1. E-mail the CLSC with the participant ID# and acrostic as soon as the participant is eligible. A set of labels will be generated for each participant. Allow 1 week for labels to be printed and shipped. Labels are provided for all tubes and vials.

2. Affix the completed labels to the appropriate tubes found in the kits before the draw. Position the labels on the 2 mL freezing vials over the white patch allowing the volume markings to remain visible.

Note: It is imperative that all tubes are labeled correctly and completely.

Prepare Forms 30 and 31

1. Use one copy of each form and its worksheet per subject per visit. Fill out the top of each form (ID and Visit) and the top of each worksheet (ID) prior to the visit.
2. The remainder of each form will be completed at the visit.

Prepare the Storage/Shipping Supplies

1. A -70°C freezer must be available for storing samples after collection and processing. Specimens will be shipped by Federal Express to the laboratories and the storage facility in batches at mutually agreeable intervals. Contact each laboratory to arrange the shipping schedule. Contact the CLCS for shipping supplies.

2. Store specimens in boxes in the freezer until each batch is ready for shipment to CLCS, Sack's lab, or the NHLBI. Complete the Central Lab Shipping log forms (form #38 and #39) when processing and freezing the samples in order to record which sample is going into the slots in the freezer boxes. These forms will accompany the specimens when shipped.

At the Visit:

General Instructions

- Treat all materials that have been in contact with blood or urine as potentially infectious. Dispose of these materials, including needles, by approved procedures for the individual site. Wear gloves to minimize the transmission of infection.

Collection of Blood Samples

- A fasting blood must be collected at SV3 and twice during each intervention period. Participants must have fasted at least 10 hours prior to blood collection, with only water allowed. If the participant has not been fasting, the visit must be rescheduled.

- Due to the sensitivity involved in specific testing, standardization of specimen collection is imperative. The subject must be seated for at least 10 minutes prior to specimen collection. A tourniquet may be used for no longer than 2 minutes. Deviation from this standardization sample collection protocol will cause significant variability in assay results. **Be consistent from visit to visit**.

- Clean arm with an alcohol pad, then draw blood from the crook of the arm, generally from the antecubital vein. Fully fill all tubes.

- Draw the three SST serum tubes before the three EDTA plasma tubes. Non-additive tubes are drawn before additive tubes to avoid additive contamination of the non-additive tube. Cross-contamination between different additive tubes can also occur, making test results erroneous.

- Thoroughly mix all tubes immediately after collection by gently inverting the tubes at least five times. **Do Not Shake**.

- Remove the needle and apply pressure to the venipuncture site. Cover with an adhesive strip when the blood has stopped flowing.

- The Central Lab Collection Form - Bloods (form #31) is used for processing the fasting blood samples.

Collection of Urine Sample

- At SV2 and before each subsequent collection period during intervention, instruct the participant to collect a 24-hour urine specimen (See appendix A for sample instructions for participants).

- 24-hour urine collection should not be done during menstruation. Schedule urine collection to avoid collections during this time.

- 24-hour urine collection should start on a Tuesday, Wednesday or Thursday. If this is not possible, start on a Friday. Starting on the weekend days should be used as a last resort. Incentives might be useful to encourage collection during the week.

- Distribute the 24-hour container and instructions to the participant and review the instructions with the participant. Attach the four labels provided to the collection jug. Complete the labels with the appropriate identifying information. If the specimen is to be returned the next day, have the participant start the collection before leaving the clinic (i.e., void the bladder into the toilet). Inform the participant to bring the container back within 24 hours of collection. Specimens should be refrigerated or kept in a cool place during collection.

- The instructions for processing the specimen should be followed no matter when the specimen is returned.

- Take the 24-hour urine container from the participant. Check to make sure that the labels on the tab attached to the jug are filled out correctly and completely, and verify that the ID listed on the label matches that of the participant.

- Confirm that the participant:
  1) voided her bladder at the start of collection and did not save the specimen
  2) collected all voids during the collection period
  3) collected a final voiding at the end of the collection period
  4) returned the specimen within 24 hours of the final voiding

- The specimen is considered to be inadequate if any of the following are true.
  - The total duration of the collection is less than 22 hours or greater than 26 hours
  - The collection period did not start with an initial, discarded voiding
  - More than one voiding (including the final voiding) was missed
  - The total volume of the sample is less than 500 cc
  - The urine is collected during menstruation

- **If the specimen is inadequate, or if the participant failed to bring it in, a second specimen must be obtained.** Give the participant a new set of collection materials, attach and fill out the labels correctly. Save an aliquot from the original sample as a backup in case the participant is not able to provide an adequate sample, and note on the label that the

sample was inadequate. If the participant does not bring a repeat specimen, analyze the aliquot from the original (inadequate) sample in its stead, and note on the shipping label that the sample was inadequate and why. If both the samples are inadequate, send the better of the two samples.

- Assuming that the participant does bring in a specimen, either immediately take it to the clinic's lab area for processing or place it in a refrigerator until it can be processed. Avoid leaving the specimen at room temperature for any longer than is necessary.

- The Central Lab Collection Form - 24-hour urine (form #30) is used for processing the 24-hour urine sample.

After the Visit:

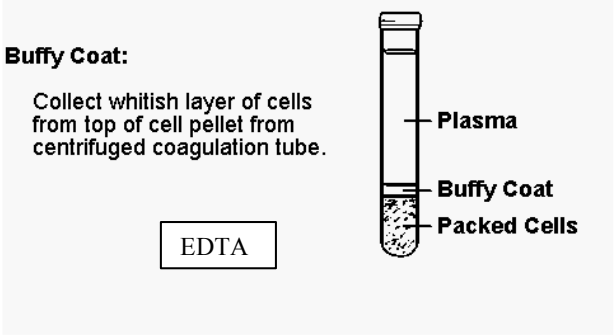
Process and Store Specimens

EDTA Plasma

1. Centrifuge the 3 x 10 mL (purple top) EDTA tubes without delay at room temperature. Centrifuge at >1,500 x g for 15 minutes to remove blood cells. No red cells should be present in the plasma or along the sides of the tubes.
2. Using a transfer pipette, transfer the plasma into the 30 mL plastic pooling vial. Cap the pooling vial and invert several times to obtain a homogeneous specimen.
3. Using transfer pipettes, transfer the plasma from the pooling vial into the 10 X 2 mL appropriately labeled freezing vials with purple caps.
4. Fasten the caps tightly and immediately place the vials in freezer boxes at -70^{o}C.
5. Fill out the Central Lab Shipping Log - Blood (Form #39) as you fill the slots in the box. Enter the participants ID# (space) Accrostic to match the preprinted label.

Note: Collect the Buffy Coat at the PI-4 visit.

- Save the EDTA tubes that contain the packed cells for the buffy coat. The buffy coat is the whitish layer of cells overlaying the packed red cells remaining in the EDTA tubes after the plasma is removed.



- Collect the buffy coats all three EDTA tubes and transfer into the 2 mL freezing vial with a clear cap labeled for "Buffy Coat."

Serum

1. Allow the 3 x 10 mL SST tubes (red/gray top) to clot for 30-60 minutes at room temperature in an upright position. Verify that the specimen is fully clotted.

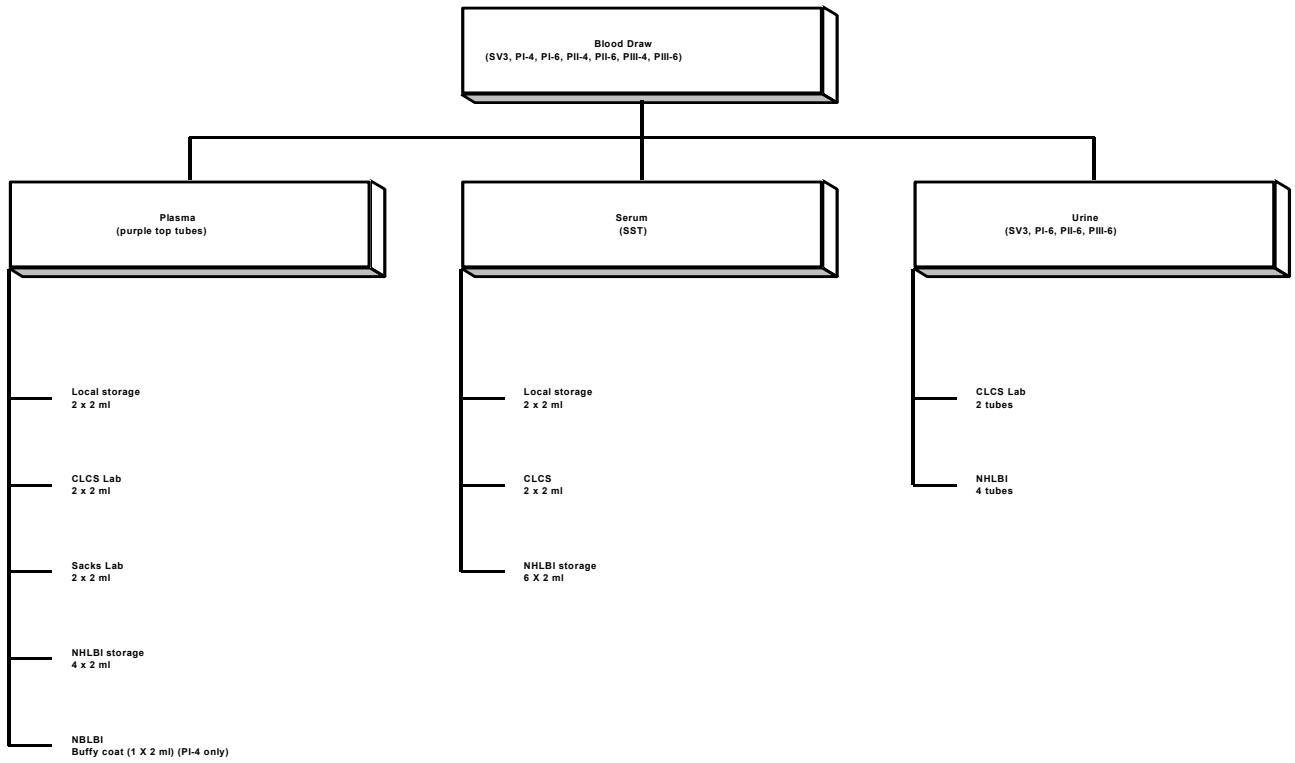
2. Centrifuge the clotted tubes for 15 minutes at 1,500 x g. After centrifugation, check the SST tubes for a complete gel barrier between the serum and the cells. Re-centrifuge if the barrier is incomplete or if red cells are seen above the barrier.
3. Pour the serum from the SST tubes into the 30 mL pooling vial. Cap the pooling vial and invert several times to obtain a homogeneous specimen.
4. Using a transfer pipette, transfer the serum from the 30 mL pooling vial into the 10 x 2 mL appropriately labeled freezing vials with red caps.
5. Fasten the caps tightly and immediately place the vials in freezer boxes at -70^{o}C.
6. Fill out the Central Lab Shipping Log - Blood (Form #39) as you fill the slots in the box. Enter the participants ID# (space) Accrostic to match the preprinted label.
7. Fill out the worksheet for the Central Lab Collection Form- Fasting Blood (Form #31)
8. Repeat draw if blood is hemolyzed or if there if tubes are destroyed during centrifugation.
9. After any repeat draws for this participant are complete, use the worksheet to complete Form #31

Note: The blood specimens are stored in 2" boxes which hold 100 x 2 mL vials (10 X 10 grid). Place samples sequentially in the box starting with the front, left corner of the box, moving to the right, then to the back as each row fills. Note sample locations on Form #39 as you fill each box.

Urine

1. Record the sample identification, dates and times on the Central Lab Collection Form- 24-hour Urine (Form #30).
2. Invert the sample container at least eight times to ensure a uniform sample.
3. Measure the total urine volume by using a (use a graduated cylinder). Note the volume on Form #30.
4. Label the 6 x 8 mL freezing vials yellow capped vials using the preprinted labels for each participant.
5. Add 5 mL of well-mixed urine to tubes 1-6, using a transfer pipette. Cap securely. Invert to mix.
6. Fasten the yellow caps tightly and immediately place the vials in freezer boxes (in an upright position) at -70°C.
7. The remaining urine may be discarded. Be sure to use distilled/de-ionized water to rinse the graduated cylinders between samples to avoid cross-contaminating the specimen.
8. Fill out Central Lab Shipping Log - Urine (Form #38) as you fill the slots in the box. Enter the participants ID# (space) Accrostic to match the preprinted label.
9. Fill out the worksheet for the Central Lab Collection Form- 24-hour Urine (Form #30).
10. If a repeat collection is necessary, repeat the steps above.
11. After any repeat collections for this participant are complete, use the worksheet to complete Form #30.

Note: The urine specimens are stored in 3" boxes (7 X 7 grid). Due to the space required by caps, the 3" urine boxes will hold 36 instead of 49 vials. The fourth position in each row and the entire fourth row must be left empty for the vials to fit. As with the 2" boxes, the starting location for filling these boxes is the front, left corner of the box, moving to the right, then to the back as each row fills. Note sample locations on Form #38 as you fill each box.


Blood Draw
(SV3, PI-4, PI-6, PII-4, PII-6, PIII-4, PIII-6)
Plasma
(purple top tubes)
Serum
(SST)
Urine
(SV3, PI-6, PII-6, PIII-6)
Local storage
2 x 2 ml
CLCS Lab
2 x 2 ml
Sacks Lab
2 x 2 ml
NHLBI storage
4 x 2 ml
NBLBI
Buffy coat (1 X 2 ml) (PI-4 only)
Local storage
2 x 2 ml
CLCS
2 x 2 ml
NHLBI storage
6 X 2 ml
CLCS Lab
2 tubes
NHLBI
4 tubes

Shipping to CLCS and NHLBI

1. Two sizes of cardboard freezer storage boxes are provided: 2" boxes for serum, plasma, and buffy coat specimens in 2 mL vials (10 x 10 grid) and 3" boxes for urine specimens in 8 mL vials (7 x 7 grid). Boxes of each size are provided for CLCS and NHLBI while Sacks' lab and local storage will only need the 2" box (10 x 10 grid). Specimens are processed and placed in the freezer boxes as previously outlined.

2. Forms 30 and 31 contain the detailed participant information for the blood and urine samples should be filled out and entered at the collection period.

3. Forms 38 (urine) and 39 (bloods) are shipping forms that are used when putting the samples into the boxes before freezing. As the samples are put into the box, note the box slot number, the participant ID# and Accrostic, the visit the sample is collected at, the collection date, the sample type (e.g., plasma, serum) and any comments about the particular sample. These forms will accompany the samples when shipped to each lab.

4. Contact the CLCS for shipping supplies at least 2 weeks prior to the scheduled ship date.

5. Instructions for packing and shipping samples will be included with the shipping supplies.

6. Contact each laboratory prior to shipping samples to arrange a shipping schedule.

Appendix A

Instructions for 24-Hour Urine Collection (Weekend collection)

To collect a 24-hour urine specimen, you will need a plastic sample container (women may also want to use a collection device referred to as a hat). The container should be labeled with your study identification number, the date and time you begin the urine collection and the date and time you complete the collection. It is important to collect all of the urine you pass during the 24-hour collection. However, if you do forget and miss a collection, it is equally important that you indicate how many voidings were missed on the tag at the end of the collection.

Women should use the hat to help collect the sample. This is done by placing the hat under the toilet seat, urinating into the hat, then carefully empty the contents of the hat into the jug. Otherwise, urinate directly into the jug. In the event of a spill, please estimate the amount spilled; write the amount on the recording tag (e.g., "1 cup spilled"). If you miss a sample, record this on the tag in the place provided.

How to collect the 24-hour urine.

Do not collect the first urine of the day, but note the time of this first morning urination on the tag of the urine container. This is the start of your collection period. Beginning with the second urination of the day, collect all urine for the next 24 hours from the time of the discarded urine. Every time you have to urinate, collect the entire sample in the container. For example, the last sample collected should be voided 24 hours after the first morning urination (the times on the recording tag might be 7:30 a.m. start time and 7:30 a.m. stop time, for example) and should also go into the container. Write the date and time of your final urination on the tag of your container. Store the container in a refrigerator or a cooler between voids if possible. Bring your sample into the center as soon as possible after collection is complete.

Instructions for 24-Hour Urine Collection (Weekday collection)

To collect a 24-hour urine specimen, you will need a plastic sample container (women may also want to use a collection device referred to as a hat). The container should be labeled with your study identification number, the date and time you begin the urine collection and the date and time you complete the collection. It is important to collect all of the urine you pass during the 24-hour collection. However, if you do forget and miss a collection, it is equally important that you indicate how many voids were missed on the tag at the end of the collection.

Women should use the hat to help collect the sample. This is done by placing the hat under the toilet seat, urinating into the hat, then carefully empty the contents of the hat into the jug. Otherwise, urinate directly into the jug. In the event of a spill, please estimate the amount spilled; write the amount on the recording tag (e.g., "1 cup spilled"). If you miss a sample, record this on the tag in the place provided.

How to collect the 24-hour urine.

You will begin your urine collection at the clinic. When you arrive at the clinic, you should void but do not collect this urine. This is the start of your collection period. Beginning with the second urination of the day, collect all urine for the next 24 hours from the time of the discarded urine. Every time you have to urinate, collect the entire sample in the container. For example, the last sample collected should be voided 24 hours after the clinic urination (the times on the recording tag might be 4:00 p.m. start time and 4:00 p.m. stop time, for example) and should also go into the container. Record the date and time of your final urination on the tag of your container. Store the container in a refrigerator or a cooler between voids if possible. Bring your sample into the center as soon as possible after collection is complete.

CORE LABORATORY FOR CLINICAL STUDIES
Washington University in St. Louis ▪ School of Medicine

Appendix B
OMNI Heart Study
Supply Request Form

Fax this form to the CLCS at (314) 362-4782.
Request Supplies 2 weeks prior to date needed.

Date Requested: _____ Requested by: _____

Site: _____ Contact #: _____

Date Supplies needed by: _____

# needed	Lab Supplies	# needed	Lab Supplies
_____	Plasma Kits	_____	Urine Kits
_____	Serum Kits	_____	Urine Jugs with Labels
_____	Buffy Coat Vials (20 vials/pkg)	_____	Urine Collection Hats

2" Freezer Box for Blood Storage Labeled:
_____ Local Lab _____ CLCS
_____ Sacks _____ NHLBI
(Indicate # needed for each)

3" Freezer Box for Urine Storage Labeled
_____ CLCS _____ NHLBI
(Indicate # needed for each)

_____Transfer Pipets (25 pipets/pkg)

Participant Labels: E-mail ID# and Acrostic to clcs@im.wustl.edu at least 1 week prior to the date needed. Label set to be used for the entire study will be sent via Federal Express. Indicate date labels are needed in e-mail request.

Shipping supplies

_____ Shipping Coolers - Indicate # of boxes to be shipped. Appropriate size cooler will be provided.
_____ # 2" Freezer Boxes to Ship _____ # 3" Freezer Boxes to Ship

Note: Shipping instructions and all needed shipping supplies will be included in the cooler.

OTHER SUPPLIES_____

Questions? Call Customer Service at (314) 362-3522

For CLCS Use
Date Request Received: _____ Initials: _____
Date Assembled: _____ Initials: _____
Date Shipped: _____ Initials: _____
Tracking #: _____

Summary Edits

8. Data Entry and Management

Staff ID's

All OMNI-Heart staff must have an OMNI-Heart staff ID number. To obtain a staff ID number, the clinic coordinator should e-mail the Data Manager at the Data Coordinating Center (DCC) with the following information:

- First and last name
- Project job title
- Address (work)
- Phone number (work)
- Fax number (work)
- E-mail address (work)

The Coordinating Center will assign a new number within 48 hours of receipt of this information.

Quality Control Methods Prior to Data Entry

The clinic coordinator will need to manually employ the quality control methods outlined below in real-time before the participant leaves the intervention site for both the batch-entered and centrally entered data. These methods include:

<u>Patient identification and record linkages.</u>

The DCC will generate the participant ID numbers. We will use a check digit mechanism to defend against digit transposition. Its construct is as follows:

Participant ID: S1 P1P2P3 D1

Where:

S1 = the site identifier 1 or 2 = BWH, 3 or 4 = Johns Hopkins

P1-3 = the patient sequence number within the organization

D1 = the check digit code:

Defined as:

D1 = Mod (S1*2+P1*3+P2*4+P3*5, 11)

If D1=10, then use D1= "A", otherwise use the digit D1.

The DCC will generate a list of individual participant identification numbers, a sequential number starting with 001. Then a check digit will be calculated and a list of up to 2000 unique participant ID's will be generated for each site (see Table 1 below). Each of the potentially eligible patients will be assigned a participant ID from the list provided by the DCC. To establish the record linkage, the lists will be formatted as logs, with space next to each participant ID to record participant initials (or name), and the participant's date of birth. The clinic coordinator's will put the patient name and date of birth on the participant ID List and then use that participant ID on all pages of all study data forms beginning with the PSV or SV1 BP form.

Table 1. Example of List of Participant ID's to be used at BWH

Participant ID	Participant Name/Initials	DOB
10009		
10014		
10020		
10035		
10041		
10056		
10061		
10077		
10082		
10098		
10105		
10111		
10126		
10131		
10147		

Legibility. All data must be checked for illegible handwritten replies, spelling errors, etc. All checked response boxes must have checks within designated spaces. Check to be sure that the forms are filled out in pen. With the exception of the Food Frequency Questionnaire (FFQ), forms filled out in pencil are not acceptable.

Form admissibility. All forms must be checked to determine if the form was completed within the specified time window. All forms must be checked to assure that the completed form is the correct one for the indicated visit or activity.

Missing information. All forms must be checked for unanswered items or sections of an otherwise completed form. The clinic coordinator must assure that all necessary forms have been completed for the indicated visit or activity before entry of the individuals visit data can begin.

Consistency. All data must be checked to assure that information supplied in one section is consistent with data in another section of the same form. All forms for the same participant for a given visit must be checked to assure consistency. Skip patterns on forms should be checked for the correct data flow.

Range and inadmissible codes. All data must be checked to assure they do not contain values either outside specified ranges or undefined alphabetic or numeric codes.

The individual coding instructions that are attached to the relevant forms provide detailed instructions for coding and review procedures for each study form. Be sure to review the coding instructions for the form before completing the review process. See the section below for details on how to correct errors on the forms.

Data Edits on Forms

It is important to use the following process when making corrections to study forms to assure the accuracy and validity of the data.

- Participant responses should never be obliterated.
- In red ink, a slash should be made through the incorrect response and the correct response written next to it.
- The reviewer's initials, date of correction and an explanation of the edit should be written next to the data field that is being edited.

For example:

~~92~~ 90 *RL 8/5/2003 Addition error*

If a participant makes a correction to a form, the clinic coordinator should

- verify that the response is clearly written.
- In red ink, slash through the old response.
- The reviewer's initials, date of correction and the notation "participant correction" should be written next to the data field.

For example:

YES **NO**

☒ ☒ *RL 8/5/2003 participant correction*

Data Entry

The site should copy the requested forms and complete the accompanying shipping log (form #36) and send to the DCC Data Manager. A summary error report and a detailed error report will be compiled for the site. The clinic coordinator and Data Manager will then work together to solve any discrepancies that may have occurred. The clinic coordinator is responsible for seeing that corrections are made to the forms if needed (see data edits on forms section). Corrected copies of the forms should be faxed or mailed to the DCC. Changes that need to be made to the database should be clearly noted on the form. The DCC will file all copies of the forms in the participant's chart.

Data Validation by the Hopkins Site

The Data Management system has several data validation reports available for the sites to validate their own forms. There are reports to view all screening data, all blood pressure data and all daily diary data for randomized participants. The clinic coordinator can print out the above reports for all randomized participants for the current cohort.

The following list is a guideline for the amount of data validation to be conducted at the individual sites:

- All screening data for randomized participants
- A random sample of daily diaries for randomized participants

The sites can also use the view feature in the Data Entry System to look at individual participant's forms. (See the OMNI-Heart Data Entry User's Manual for details.)

Archiving

For the Hopkins site, a copy of the MS Access Omni-Heart database will be transferred daily via e-mail to the coordinating center's data manager. Archiving will occur at the coordinating center, and will contain the previous day's data on-line and all historical data off-line. For reasons of safety and backup, archives of the Omni-Heart database will be stored on the Channing Laboratory computer network. The historical data is easily obtained if restoration is needed. In addition, all data collection forms need to be archived for the life of the study in hard-copy form so that copies may be sent to the coordinating center as needed for data management. Requests for copies of archived data will be made on a form-by-form basis by the DCC.

Summary of Edits

9. Trial Monitoring Reports

Introduction

During the trial's course, the Data Coordinating Center produces a variety of reports to help the Steering Committee, Measurement Committee, Recruitment Committee, Clinic Coordinators, and the DSMB monitor the progress of the trial.

Additional reports, produced for the DSMB only, permit the DSMB to monitor the efficacy and safety of the interventions. These reports include not only standardized reports issued at regular intervals but also ad hoc reports as requested.

The reports prepared for the Steering Committee focus on the recruitment of participants into the trial. These reports allow the Steering Committee to ensure that recruitment is proceeding in a timely manner and to identify potential recruitment problems at an early enough stage that they can be corrected. In addition, the Steering Committee also receives reports summarizing the completeness and quality of the study database.

The Measurement Committee receives the same reports as the Steering Committee. The other committees receive reports relevant to their areas of expertise.

Types of Reports

Recruitment/Follow-up Reports

Recruitment and follow-up reports summarize recruitment activity and follow-up to date. These reports assist field sites in meeting recruiting needs and in scheduling eligible participants for upcoming screening visits.

Baseline Data Reports

These reports present the baseline characteristics of the randomized participants. Data are presented both by site and by treatment order. All of the information reflects baseline, pre-intervention data and therefore should be comparable across treatment groups.

Quality Control Reports

Quality control reports include a number of reports related to the integrity of the Omni-Heart database and adherence to trial protocol by both participants and sites. These include audit reports, counts (observed/expected) of data collection items and visits, with a particular focus on outcome variables.

Laboratory QC and Results Reports

Laboratory quality control reports summarize lab tracking, including receipt, receipt status, and the collection of process measures such as start and stop times for 24-hour urine samples

Serious Adverse Events Report

This report will list all serious adverse events that occur. An unblinded version of this report will be made available to the DSMB.

Side Effects Report

The side effects report summarizes side effects reported by Omni-Heart participants during the course of the study.

Outcome Measures and Safety Issues Reports

These reports are only sent to members of the DSMB. They comprise unblinded study data.

Distribution of Reports

Monthly Steering Committee/Measurement Committee Reports

These are generally distributed by uploading to the WWW site and notifying committee members by e-mail prior to the meeting or conference call.

- Recruitment/Follow-up Reports
- Baseline Data Reports
- Quality Control Reports
- Laboratory QC and Results Reports
- Side Effects Report

Monthly Recruitment Committee Reports

Distribution will be via the WWW site with notification to investigators when updates occur.

- Recruitment/Follow-up Reports

End of Cohort Reports

These are distributed to the Steering and Measurement Committees at the end of each cohort after all data have been entered.

- Recruitment/Follow-up Reports
- Baseline Data Reports
- Quality Control Reports
- Laboratory QC and Results Reports
- Side Effects Report

Reports for DSMB Meetings

These are prepared and distributed about 2-4 weeks prior to each DSMB meeting.

- Recruitment/Follow-up Reports
- Baseline Data Reports
- Quality Control Reports
- Laboratory QC and Results Reports
- Side Effects Report
- Outcome Measures and Safety Issues Reports

Summary of Edits

10. Safety Monitoring

Blood Pressure

In order to prevent a prolonged period of untreated hypertension (outside the eligibility range of OmniHeart), several blood pressure safety procedures are observed.

- At PSV, individuals taking any anti-hypertensive medications are excluded, and those who report having taken them in the past must have been off of them for at least two months.
- Individuals with a history of cerebrovascular or cardiovascular disease are excluded, as are those with congestive heart failure
- Blood pressure is monitored regularly throughout the study, and "escape levels" are established to identify, and ensure proper follow-up of individuals with an elevated blood pressure that might warrant drug therapy. Participants may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment even though the BP is below the escape thresholds.
- Individuals who complete the study with persistently high, but still allowable, blood pressure readings are referred for counseling and possible treatment as part of the close-out visit.
- If escape levels are reached or a participant is referred for BP management for some other reason, a BP Escape Tracking Record (Form #23) is filled out. This form is used to document responses of the OmniHeart investigators and contacts with personal providers to each escape level blood pressure. Once the form is complete, a copy is sent to the DCC.

OMNIHEART Blood Pressure Escape Criteria

The following blood pressure escape levels and protocols have been established to ensure that participants are offered appropriate evaluation and therapy when clinically indicated. The actions taken when these escape levels are reached vary somewhat for screening, run-in, and intervention. In all cases, participants may be immediately referred for evaluation if a clinician believes such action is appropriate based on his or her own clinical judgment.

Screening

Screening criteria for excluding participants from further participation based on elevated blood pressure levels are discussed in sections 7 and 8 of the protocol. In the event that the mean SBP at any one visit exceeds 180 mm Hg or the mean DBP exceeds 110, the participant is not only excluded from the study but is referred to a physician to determine if medication is needed. If the participant does not have a personal physician, qualified personnel at the clinical center may make the recommendation for treatment.

Run-In Feeding

Two escape levels apply during run-in and intervention feeding. They differ in terms of the frequency with which a follow-up measurement is required. Also, a repeat elevated blood pressure triggers an automatic exclusion during run-in but only a referral during intervention feeding.

Escape level #1: The mean blood pressure recorded at any single visit exceeds either a SBP of 180 mm Hg or a DBP of 110 mm Hg.

Action: Participant may be excluded immediately and referred to a physician for further evaluation. Alternatively a second blood pressure measurement must be obtained within four days and prior to randomization. If this second measurement exceeds 170/105 mm Hg, the participant is automatically excluded and referred to a physician for follow-up.

Escape level #2: The mean blood pressure recorded at any single visit exceeds either a SBP of 170 mm Hg or a DBP of 105 mm Hg.

Action: Participant may be excluded immediately and referred to a physician for further evaluation. Alternatively a second blood pressure measurement must be obtained within four days and prior to randomization. If this second measurement exceeds 170/105 mm Hg, the participant is automatically excluded and referred to a physician for follow-up.

If the participant does not have a personal physician, qualified personnel at the clinical center, ideally blinded to randomization assignment, may make a recommendation for treatment.

Intervention Feeding

Escape level #1: The mean blood pressure recorded at any single visit exceeds either a SBP of 180 mm Hg or a DBP of 110 mm Hg.

Action: A second blood pressure measurement must be obtained within four days. If this exceeds 170/105 mm Hg, the participant is referred to a physician for follow-up.

Escape level #2: The mean blood pressure recorded at any single visit exceeds either a SBP of 170 mm Hg or a DBP of 105 mm Hg.

Action: A second blood pressure measurement must be obtained within seven days. If this exceeds 170/105 mm Hg, the participant is referred to a physician for follow-up.

If the participant does not have a personal physician, an investigator at the center, ideally blinded to diet status may make a recommendation for treatment.

In the event that a participant is referred to a clinician for evaluation, the clinical center should seek to obtain a set of up to five end-of-intervention blood pressure measurements. Care should be taken, however, that this does not delay or otherwise interfere with appropriate clinical care. If blood pressure medication is not initiated, the participant continues in the trial.

Referral for Non-Blood Pressure Reasons

Abnormalities noted in laboratory or physical assessments that require medical evaluation result in referral to other medical care sources unless they arise as a direct result of participation in OMNIHEART. If clinical problems arise from OMNIHEART participation, the problem may be dealt with at the clinical center or through referral as is most appropriate.

Morbid Events Affecting Blood Pressure

Participants who suffer a morbid event with a lasting effect on blood pressure (e.g., myocardial infarction, stroke) are considered terminated as of the date of the morbid event. ***Similarly, participants who are placed on exclusionary medications or special diets by their physicians are also considered terminated as of the date these medications or diets began. In each of the above cases, the participant's end-of-intervention blood pressures are calculated as outlined in section 4.11 of the Protocol and he/she is excluded from further participation in the study.****

Approach to Participants Placed on Anti-Hypertensive or Cholesterol-Lowering Medications

During the course of the trial, some randomized participants may start either anti-hypertensive medication or cholesterol-lowering medication.

Food Safety

Clinic staff are instructed in procedures for handling, preparing, and distributing foods. These procedures focus on preventing contamination of foods and on safe preparation, storage, and consumption practices. Participants are instructed to immediately report symptoms that may arise from food-borne illness. Such reports trigger clinics to investigate whether other participants have experienced similar symptoms, to review their own procedures, and to determine if further action is required. In order to avoid food-borne illness, participants are provided instructions on food storage and preparation.

Adverse Events, including Serious Adverse Events

Throughout the run-in and intervention feeding periods, the Daily Diary (Form #24) is used to capture information about symptoms from the study foods and about intercurrent medical events. Symptoms of lactose intolerance and to other gastrointestinal symptom will typically be addressed by a study dietitian. The daily diary is also meant to capture intercurrent medical problems that would be classified as a serious adverse event. Serious adverse events include any of the following:

Fatal or life-threatening event
In-patient hospitalization
Prolongation of existing hospitalization
Significant or persistent disability
Congenital abnormality or birth defect
Any other event that may adversely affects the rights, welfare or safety of the participant.

If a serious adverse event occurs, the staff member should notify the principal investigator or designated study clinician, should gather some basic information, and should complete Form 12 (Serious Adverse Events). The study clinician should review and sign this form and if appropriate contact the participant. The study clinician should then complete the bottom of Form 12 and the corresponding local IRB form used to document serious adverse events. The clinician should submit the report to the local IRB according to their guidelines and send copies to the DCC and the NHLBI project officer. The DCC will collate these documents and report to the Steering Committee and the DSMB.

Data, Safety and Monitoring Board

An external Data and Safety Monitoring Board (DSMB) reviews the trial's progress at least on an annual basis. Their review includes unblinded interim results. The DSMB can recommend that the NHLBI terminate the trial early if participants are being subjected to undue risk or if the trial's objectives are met and further follow-up would serve no added scientific purpose.

Laboratory Abnormalities

Participants are provided with a copy of local laboratory studies. Also, they are informed of any clinically significant, local laboratory abnormality, whether or not these constitute an exclusion to OMNIHEART. These laboratory data are supplied to the participant and, with his/her permission, to his/her physician for follow-up.

11. Participant Closeout

Participant Closeout

Purpose

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

Closeout Prior to Randomization

If a participant refuses to participate in the study or becomes ineligible prior to randomization, they need to be closed out of the OMNI Heart data entry system.

Eligible participants who decline enrollment: If a participant declines enrollment in the study, they can be closed out by using the Participant Closeout/Termination Form, (Form #18, Section A.). Check the primary reason that most accurately describes why the participant did not enroll.

Participants who become ineligible prior to randomization: If refusal/ineligibility is determined prior to randomization, the participant can be closed out by using the Participant Closeout/Termination Form (Form #18, Section B.). Check the primary reason that most accurately describes why the participant is ineligible.

Early Termination After Randomization

Post-Randomization termination: If a participant terminates study participation after being randomized they can be closed out by using the Participant Closeout/Termination Form (Form #18, Section C.). Check the primary reason that most accurately describes why the participant is terminating their study participation.

Note also that for anyone who drops out of the study after having completed week four of the first intervention period, for whatever reason, OMNI Heart personnel should try to obtain as many of the five end-of-feeding period blood pressure measurements as possible, along with a fasting blood draw for that intervention period and any remaining interventions for that participant.

End of Cohort Closeout

At the conclusion of each cohort, closeout activities take place in the context of a group session. Study participants receive a summary of their average screening blood pressure measurements and the average of all their blood pressure measurements during the three diet periods. The participants are not informed of their intervention group status and individual blood pressure measurements until the end of the entire study. While the structure and content of the close-out activities is left largely up to the individual sites, the following must occur:

- Provide summary of screening blood pressure averages and the average of all their blood pressure measurements during the three diet periods
- Distribute education materials including, but not limited to:
  - -The DASH Eating Plan
  - -Your Guide to Lowering Blood Pressure
- Give certificate and/or letter of appreciation
- Review "What's Next in OMNI Heart?" handout (Appendix 1)

End of Trial Closeout

Data Management

The final closing out of participants from the OMNI Heart data management system will occur when all data collection forms from a participant are collected and entered into the OMNI Heart data entry system. The Intervention Flow Form (Form #20) for PIII should be completed and entered.

Unblinding

At the conclusion of the entire trial, the clinical centers will provide additional information to participants beyond that provided at the end of cohort closeout. Such information can be provided in the context of a meeting or mailing. In either instance, include a summary of trial results and information specific to the individual. A general description of the diet in lay terms is provided. At this time, participants also receive a listing of their individual blood pressure responses to each intervention.

Appendix 1.

What's Next in Omni Heart?

April 2005

- Last group will finish feeding
- Last data will be sent for analysis
- Last blood and urine samples will be sent for analysis

May to October 2005

- Study results will be analyzed

November 2005

- You will receive a detailed report with your personal results, including:
  - Your blood pressure on each diet
  - Your cholesterol and triglyceride levels on each diet
  - Your weight
  - Your diet assignments

- Final Farewell Reception. You will be invited to a reception to hear the study results, discuss what they mean, and ask questions.

Spring - Summer 2006

- A reprint of the main trial results will be mailed to you.