DASH2 Clinical MOP

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Summary of Edits

1. Trial Administration and Personnel

DASH2 is a cooperative agreement in which the NHLBI Project Office, participating clinical centers, and the coordinating center (CC) act together to design a common protocol and administer the trial. The Steering Committee is the primary decision making body for the trial. Standing subcommittees include: design and analysis, recruitment, measurement and quality control, diet, and publications and ancillary studies. An independent Data and Safety Monitoring Board (DSMB) also serves the study. The functions of these committees and of the DSMB are given in the Protocol and are summarized below.

The lead Project Scientist representing the Project Office is Dr. Eva Obarzanek. The coordinating center is housed at the Kaiser Permanente Center for Health Research in Portland (Dr. William Vollmer, PI). The four clinical centers are: Brigham and Women's Hospital in Boston (Dr. Frank Sacks, PI), Johns Hopkins University in Baltimore (Dr. Larry Appel, PI), Pennington Biomedical Research Center in Baton Rouge (Dr. George Bray, PI), and Duke University Medical Center in Durham (Dr. Laura Svetkey, PI). The Food Analysis Laboratory Control Center of Virginia Polytechnical Institute and State University in Blacksburg (Dr. Katherine Phillips, PI) and a central laboratory for analysis of blood and urine specimens are contracted through the coordinating center.

Steering Committee

Membership

Members: Principal and co-investigators at the coordinating center and at each clinical center, the chair of the diet and clinic coordinators subcommittees, and the members of the Project Office

Chair: Frank M. Sacks, MD

Vice Chair: Laura P. Svetkey, MD

Voting: One vote for each of: Project Office, coordinating center, and each clinical center

Functions and Responsibilities

- Assures clear delineation of roles and responsibilities among participating institutions.
- Reviews and approves all policies, protocols, and trial-wide procedures.
- Monitors performance of DASH2 overall and of each clinical center, including recruitment, adherence, data collection, quality control, and data analysis.
- Considers and approves any ancillary studies and access to study data.

- The Steering Committee meets face-to-face at least semiannually, with conference calls or additional meetings as needed and with regular sharing of information. Meetings are open to all study personnel. Conference calls should include at least the PI (or designee) from each site, project officer, chair of Diet Committee and subsequent chair of Clinic Coordinator committee after it convenes.

Clinic Coordinators

Chair: Kathy Aicher

Functions and Responsibilities

- Serves as primary liaison at sites when communicating with CC on issues of data management and quality assurance.
- Advises the Steering Committee on issues relating to clinic operations.

Design and Analysis Committee

Chair: Frank M. Sacks, MD

Functions and Responsibilities

- Recommends to the Steering Committee the basic design components of the trial
- Recommends changes in, and additions to, the Protocol regarding design and analysis issues during implementation as appropriate.

Measurement and Quality Control Committee

Chair: William M. Vollmer, PhD

Functions and Responsibilities

- Recommends to the Steering Committee study measurements, processes, and procedures for assuring quality control of the trial, including training, certification, quality control measures and procedures, and other activities directed at assuring that the data are valid and reliable.

Diet Committee

Chair: Pao-Hwa Lin, PhD, RD

Functions and Responsibilities

- Recommends to the Steering Committee policies, practices, and procedures relating to development, assay, analysis, procurement, preparation, delivery, consumption, and assessment of adherence of the various diets.

Recruitment Committee

Chair: Larry J. Appel, MD

Functions and Responsibilities

- Facilitates the successful recruitment of study subjects
- Assists in developing recruitment materials
- Provides input on prescreening activities
- Monitors and reports on recruitment progress to the Steering Committee
- Recommends actions to be taken to correct poor recruitment

Publications and Ancillary Studies Committee

Chair: Laura P. Svetkey, MD

Functions and Responsibilities

- Develops a written policy on publications and presentations and oversees the implementation of these policies
- The committee reviews and recommends approval of manuscripts for submission to journals for publications
- Recommends policies for the conduct of ancillary studies and reviews and recommends ancillary study proposals.

Data and Safety Monitoring Board

Membership

Chair: TBN

Members: Jeremiah Stamler, MD
Janice Derr, PhD
Richard H. Grimm, MD, PhD
Richard D. Mattes, PhD, MPH
Lemuel Moyé, MD, PhD
Jackson T. Wright, Jr., MD, PhD

Ex-Officio: Eva Obarzanek, PhD, RD
Denise G. Simons-Morton, MD, PhD
Jeffrey A. Cutler, MD, MPH
Frank M. Sacks, MD
Laura P. Svetkey, MD
William M. Vollmer, PhD
Pao-Hwa Lin, PhD, RD

Functions and Responsibilities

An independent Protocol Review Committee (PRC), appointed by the NHLBI director and chaired by Dr. Jeremiah Stamler, reviewed the Protocol prior to implementation. The PRC provided advice to the Institute regarding the scientific merit of the Protocol and made recommendations to improve the Protocol and its implementation.

Subsequent to the review and approval of the Protocol, a Data and Safety Monitoring Board (DSMB), composed of members of the PRC, is established. The purpose of the DSMB is to serve in an advisory capacity to the Institute in order to monitor, review, and assess the progress of the study (including significance of study results). The DSMB has access to unblinded outcome data during the trial and, in order that participants are not exposed to unreasonable or unnecessary research risks, recommends early termination of one or more arms of the trial if (1) the data suggest significant adverse risk to participants in the trial or (2) the specific aims of the trial appear to have been answered. The DSMB also reviews the timeliness of recruitment and data quality, based on data monitoring reports and other materials submitted by the coordinating center, and suggests analyses to be included in data monitoring reports.

The DSMB meets at least annually throughout the trial after the Protocol has been approved. In addition to the PRC or DSMB members, meetings are attended by representatives from the coordinating center, the Steering Committee (the study chair, study vice chair, and diet committee chair), and the NHLBI. Only the PRC or DSMB members may vote.

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Summary of Edits

New changes in version 1.1
Revised PASC procedures:

- Correction in wording on page 7, Approval of Manuscripts, second paragraph, last line. 1/5/98
- Modification of procedure for notifying proposers of PASC decisions, last paragraph p.2 7/2/98 CC now notifies proposer and PASC chair of results of PASC voting on proposed projects. PASC chair notifies CC if project requires discussion of questions or concerns.
- PASC members inform potential authors at their sites of new writing projects and remind authors to contact conveners directly
- Designated alternates for PASC members are not required, but may respond to abstract and MS approvals for PASC members
- Representation from each site on writing projects is encouraged but not required
- If analyses were done locally and not checked by the CC, authors must add note so stating
- As local IRBs approve ancillaries, copy of IRB approval letter and any additional consent forms must be sent to the CC
- PASC chair may require a second PASC review if the Project Office recommends substantive revisions to completed manuscripts
- Updated Figure 2.1 to reflect these changes.

Changes in version 1.2

- Procedures updated to reflect web technology.
- The assignment of a CC statistician to each paper was added to the text and to Figure 2.1.
- The exploratory phase of data analysis was added to the text and to Figure 2.1.
- Details of the paper monitoring process were added.
- Details on accessing stored laboratory specimens were added.

2. Trial Policies

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

Protocol

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

Manual of Procedures

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

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

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

Protocol and Procedure Exceptions

It is the policy of the DASH2 Steering Committee not to allow exceptions to the procedures laid out in the study Protocol and Manual of Procedures. Investigators wishing exceptions should instead petition the Steering Committee to amend the Protocol and/or MOP to formally allow the exception.

Nonetheless, unusual circumstances will arise where this procedure is not practical. In these instances the PI or designee can petition the principal investigator of the Coordinating Center, or his designee, to grant the exception. This decision can further be appealed to the full Steering

Committee. The Coordinating Center will maintain and regularly circulate a list of allowed and disallowed exceptions, as well as a list of clarifications to the Protocol and MOP.

Institutional Review Board (IRB)

The Coordinating Center and each clinical center must obtain permission from its local IRB to conduct the study before beginning recruitment. As noted above, all changes to the Protocol must also be submitted for IRB review and approval according to local IRB guidelines.

Provision of Medical Care to Participants

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

Disclosure of Study Results

Participants are blinded to their study blood pressure data during the intervention phase of the study. Participants are alerted, however, if their blood pressure goes above a predetermined escape level.

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

At the conclusion of each feeding cohort (run-in plus three intervention feeding periods), study participants receive a summary record of their study blood pressures and are given individualized counseling for reducing coronary heart disease risk. At the conclusion of the full trial, study participants are informed of their treatment assignment, receive a summary of their individual study blood pressures and selected laboratory data, and are informed about the overall findings of the trial.

Publicity

Unpublished results derived from DASH2 data may not be discussed or released without authorization of the Steering Committee. The PASC will recommend to the SC general guidelines for the content and timing of news releases and interviews for presentations and publications. DASH2 investigators may discuss design and recruitment issues with the media, but should inform the Steering Committee of any DASH2-related information scheduled for release in the national media.

Publications

Scope of the Guidelines

This policy covers papers, abstracts, posters, and oral presentations involving data collected as a part of the DASH2 study. These policies will remain in force until January 31, 2007, or until the Publications and Ancillary Studies Committee (PASC) is formally dissolved. The PASC consists of each principal investigator or his/her designee and an NHLBI Project Scientist. Other DASH2 investigators may also participate. The following overview describes the four phases of the process for producing a paper:

Phase I. Initiation and Approval of a Writing Project

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

a) A member of the DASH2 project may complete a Proposal for a DASH2 Paper (Form #72)

b) The PASC may also appoint a writing group to work on a specific publication.

2. A member of the DASH2 project completes Form #72 (Proposal for a DASH2 Paper), which specifies the research question(s) and the primary variables to be used in the analysis. The individual who completes this form is termed the "convener."

3. The convener, after adding known interested authors from his/her own or other site(s), transmits copies of the form to the Coordinating Center and to the PASC Chair. The CC will circulate the proposals to the PASC members for approval via the DASH2 web site. Paper ballot may still be used in certain situations. As soon as the proposals are posted on the web site, PASC members will be notified that a new proposal is ready for online voting. After reviewing Form #72 via the DASH2 web site, PASC members can then cast their vote. If a paper ballot is used, the CC circulates the Form #72 along with Form #73 (PASC Review Form for a DASH2 paper) to the PASC members for approval. PASC member is responsible for circulating information about the proposed manuscript to potential authors at his/her site and including names of interested co-authors on Form #73.

   Writing project proposals submitted to the PASC must be reviewed promptly. PASC members review the proposal, and vote online or sign and return the completed Form #73 to the CC within 14 days. Nonresponse is considered to be approval. PASC members who are out of town can delegate responsibility for their vote.

4. Once the voting deadline is reached, the CC informs the convener and the PASC Chair whether or not the proposed paper has been approved. If not approved, the PASC Chair discusses questions or concerns raised by reviewers on the Form #73 with the convener. The convener responds to the PASC Chair with a revised request or with a written response to the concerns, and sends a copy to the CC. The PASC Chair decides if the response satisfies the concerns, or may defer approval until the PASC can discuss the

issues in a ***conference*** call***, via e-mail,*** or ***in a face-to-face*** meeting. The PASC Chair notifies the CC whether or not proposed projects requiring discussion are approved.

5. The CC maintains and distributes a list of approved papers. Each approved paper is assigned a number and a short title that should be used on all correspondence related to the paper.

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

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

8. The writing group chair notifies the CC that the group has convened and a chair has been selected, and also confirms the membership of the writing group. See Figure 2.1 for an outline of the writing group formation process.

Phase II. Writing Group Formation and Exploratory Analysis

1. After a paper is approved, a lead statistician from the CC will be assigned to the paper. The lead statistician will contact the lead author prior to the first call to discus any exploratory analysis that can be done prior to the first call.
2. The convener sets up the first conference call or meeting of the writing group. At this first call/meeting, the writing group selects a chairperson from among its members. The chairperson serves as the first author on the paper, and is responsible for reporting progress on the paper to the CC at regular intervals
3. The lead statistician will continue to work with the lead author and the writing group doing exploratory analysis. The goal of this phase is to define all the analysis, tables, figures, etc., that will be needed for the paper. Exploratory analysis will NOT have any code review done. It is important to remember that the numbers generated in this phase are preliminary and should NOT be used in the manuscript.
4. The last stage in the exploratory phase will be for the statistician and lead author to develop one or more “formal” data analysis requests to submit to the CC.

Phase III. Formal Analysis and Writing:

1. All “formal” data analysis requests should be sent to the lead analyst at the CC. The lead analyst will call and review/clarify each request with the requestor and/or statistician (including reviewing timelines) if needed.

2. The CC will assign an analyst to the request. Once the analyst is assigned, the requestor and/or statistician will work directly with them. It is important to note that multiple analysts may be assigned to multiple requests within a paper. This is done to maximize the analysts time and to speed up getting all requests back to the authors.
3. An analysis request tracking number will be assigned to all requests. All printouts and tables will be labeled with this number. It is important to refer to this tracking number when working with the coordinating center on this request. Similar requests could be happening simultaneously and we want to be sure we are clear in our communications. It is also important to note the analysis request tracking number when using the numbers in your manuscript. When it is time for the CC to verify the numbers in the manuscript, all the numbers in the text, tables and figures need to have a reference back to the original data request.
4. All "formal" data analysis requests will be coded and stat reviewed.
5. The paper will stay in the analysis and writing phase, until the lead author has determined that all analysis and writing is complete.

Phase IV. Submission, Publication, and Archiving:

1. Number verification: The first step in this phase is to contact the lead author to send a copy to the CC of the completed paper with all data request tracking numbers annotated in the text and on all tables and figures. This is very important. The CC will be unable to verify a manuscript unless it is clearly annotated. It is best to put the tracking numbers in your manuscript as you add the numbers. It can be very difficult to go back and find the request tracking numbers associated with the numbers in the manuscript after it is written.
2. Manuscripts need to be submitted to the PASC committee and NHLBI for approval. NHLBI needs to review all manuscripts but only need to approve those where a NHLBI author is on the paper. Final revisions are made.
3. Manuscript is submitted for publication. The author needs to supply the CC with a copy of the submitted manuscript. Journal comments are addressed. Author notifies PASC chair and CC of acceptance or rejection of manuscript.
4. The author supplies CC with a copy of the published manuscript. The CC distributes copies of the published manuscript to PI's and the Project Office.
5. The CC archives all documentation, programs, and datasets needed to reproduce the analyses used in the paper.

Data Request and Paper Monitoring

After each formal data request is reviewed and an analyst assigned, the CC notifies the requestor of the projected number of hours and timeline for completion of the request. This is based on the complexity of the request, the availability of appropriate staff, and the priority of the request. The priorities are set based on the paper priorities assigned by the SC, the amount of work already done on a paper, and where in the process the paper is. It is recognized that timelines may change from initial estimates due to unanticipated difficulties or competition from requests with higher priorities. The CC will notify the lead author and statistician of any change in timeline.

Each week, during the CC priority setting meeting, the statistician and/or analyst provides an update on the status of each approved paper and analysis request. On a monthly basis, the CC sends a DASH2 Manuscript Progress Form to each lead author requesting an update on any progress. The status of all approved papers and ancillary studies is reported on the Paper Milestones Report that can be found on the DASH2 web site. The CC publishes an updated version monthly.

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

Approval of Abstracts

Abstracts of DASH2 results intended for presentation at scientific meetings should be sent directly to members of the PASC and to the Project Office along with a completed Form #77 (DASH2 Abstract Review Form), for approval prior to submission. A copy is also sent to the lead analyst at the CC for numbers verification. The sites and the CC must receive these abstracts at least five working days prior to the intended date of submission. Members of the PASC and the Project Office must respond (using Form #77) within three working days of receipt of an abstract. Designated alternates will respond on behalf of PASC members or Project Office representatives who are unavailable. Non-response within 3 days is considered approval. The CC must verify all numbers on the abstract prior to approving the abstract request.

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

Approval of Manuscripts

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

A copy of the manuscript and a completed Manuscript Review Form (Form #78) should be sent to the Coordinating Center, which in turn forwards two copies to the NHLBI Project Scientist and one copy to each member of the PASC for review. The NHLBI Project Scientist submits the manuscript for NHLBI internal review, which can require up to six weeks. All manuscripts must be received by NHLBI. NHLBI internal review and approval is required only if there is an NHLBI author. Although PASC approval and Project Office approval may be requested simultaneously, the PASC chair may require a second PASC review if the Project Office recommends substantive revisions.

The members of the PASC must respond in writing (using Form #78, DASH2 Manuscript Review Form) within 30 days of receipt of the manuscript to the PASC Chair, who will relay comments to the chairperson of the writing group and to the coordinating center. Designated alternates can respond on behalf of PASC members who are out of town. Non-response by a PASC member is assumed to be an approval.

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

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

Acceptance of Abstracts and Manuscripts

The main author sends a copy of the submitted abstract and submitted manuscript to the CC, and, if further revisions were made to the manuscript, a copy of the final version. It is the responsibility of the first author of any manuscript, abstract, or presentation to notify the PASC Chair and the CC of the acceptance or rejection of the paper, abstract, or presentation. After publication the main author shall send to the PASC Chair and the CC a copy and the appropriate citation for any published abstract and a reprint and citation for any published manuscript. The CC will distribute a copy of the published abstract or manuscript to the PIs. It is the responsibility of individual PASC members to distribute copies of abstracts and manuscripts to other investigators at their sites. The CC distributes regular reports of publications and presentations. Investigators are encouraged to share copies of slides and handouts. Hard copies of data slides and handouts to be presented at national meetings should also be circulated to the PASC Chair and the CC for distribution to other DASH2 investigators. The coordinating center maintains copies of all the slides it receives, and makes them available to other investigators upon request.

Authorship

Authors who participate in the writing of a manuscript from the DASH2 project do so in accordance with the International Committee of Medical Journal Editors guidelines (*N Engl J*

Med 1991;324:424-8)(see Appendix 2.1). First authors are expected to delete names from the final list of authors if those individuals have not participated in the writing and/or analysis of the paper in accordance with those guidelines. Unless prohibited by journal policy, all papers (excluding those resulting from ancillary studies) should include the words "DASH2 Research Group" in the authorship line, even if the analyses were not done by the CC. If analyses were done locally and not checked by the CC, a note must be added stating that analyses were done locally, e.g. "all analyses were conducted locally and not by the Coordinating Center." The SC may allow exceptions to this policy. All papers should also include an "Acknowledgments" section that lists the DASH2 investigators and key staff at the Clinical and Coordinating Centers and Project Office unless journal policy prohibits publication of such a list. In general, at least one representative from each participating institution (i.e., Clinical Centers, Coordinating Center, and Project Office) should be included as an author on papers using study-wide DASH2 data. However, membership from each site is not required.

First authors will usually be DASH2 investigators or individuals who are substantively involved in the design or conduct of the study. Others may serve as first authors if:

- the opportunity of first authorship on a project has been offered to all DASH2 investigators and none requested to serve as first author,
- at least one other DASH2 investigator serves as a co-author and "sponsor" of the project, and
- the fellow or scientist has played a major role in the data analysis and writing for the paper.

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

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

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

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

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

Figure 2.1: Outline of DASH2 Process for Producing a Paper

Phase I: Initiation and Approval of a Writing Project

DASH2 investigator proposes paper
PASC members review proposal, inform potential authors at their site, and vote
CC notifies convener and PASC chair of outcome
CC assigns statistician

↓

Phase II: Writing Group Formation and Exploratory Analyses

Convener works with assigned statistician to prepare for first call
Writing group convened, writing group identifies chair; Writing group chair informs CC of group membership/chair
Writing group chair works with assigned statistician on exploratory analyses
Writing group chair and assigned statistician generate formal analysis requests

↓

Phase III: Formal Analysis and Writing

Requests sent to CC Lead Analyst; Analyst is assigned to each request
Analyses completed and reviewed; Results or data release sent to writing group chair

↓

First Draft

Writing group reconvened
Chair prepares outline of manuscript and distributes writing assignments
First draft completed and circulated for review

↓

Subsequent Drafts

In consultation with assigned statistician, additional analyses may be specified
Requests sent to CC Lead Analyst; Analyst is assigned to each request
Analyses completed and reviewed; Results or data release sent to writing group chair
Manuscript draft recirculated to writing group.

↓

Phase IV: Submission, Publication, & Archiving

Annotated manuscript submitted to Lead Analyst at CC for numbers verification
Manuscript submitted to PASC for approval
Manuscript submitted to NHLBI for review (or approval if NHLBI author on paper)
Final revisions made

Submitted to Journal

Manuscript submitted for publication; author supplies CC with copy of submitted manuscript
Author notifies PASC Chair and CC of acceptance or rejection of manuscript

↓

Paper Published

Author supplies CC with a copy of the published manuscript;
CC distributes copy of published manuscript to PIs and Program Office
CC archives all programs and datasets for the paper

Ancillary Studies

All studies of participants enrolled in the DASH2 project that are not part of the main protocol, including proposals to analyze stored specimens, must be approved by the PASC prior to enrolling participants and collecting data. In order to obtain approval, the investigator wishing to do an ancillary study must complete and submit the Ancillary Study Request Form (Form #74) to the CC for circulation to the PASC Committee. **PIs are responsible for ensuring IRB approval for ancillary studies at their site. If a proposal is subsequently submitted for IRB approval, copy of the final approval letter from your IRB must be sent to the CC, which maintains a centralized file of all such approvals for archival purposes.** The PASC reviews the proposal within two weeks. The primary purpose of this review is to ensure that the ancillary study will not interfere with recruitment, intervention or data collection for the main study. The PASC may make suggestions for modification in order to assure that the ancillary study meets the non-interference criterion. The PASC may refuse to approve ancillary projects that appear to interfere with conduct of the main trial.

All ancillary studies approved by PASC must then be approved by the Steering Committee. The CC maintains a listing of approved ancillary studies and periodically provides a copy to the DSMB.

Access to Stored Laboratory Specimens

DASH2 will store a variety of frozen blood, urine, and buffy coat samples from DASH2 participants. Proposals to use these samples as part of an ancillary study should be submitted to the DASH2 Steering Committee in writing using the Ancillary Study Request Form (form#74). These proposals should include the type of study/test proposed, the amount of each sample required to conduct it, the rationale for the test, the study questions and hypotheses to be addressed, the plans for publication of the data, the approximate cost of the proposed test(s), and the source of funds to conduct them. Study investigators not involved in the initial proposal may request to be included in the working group conducting the additional studies.

The discussion of whether to permit use of the stored samples should include attention to possible alternative uses of limited materials. That is, the Steering Committee will attempt to plan for optimal uses of the stored samples rather than simply to grant requests for their use on the basis of which were submitted first. Any analysis of biological specimens must be approved by each center's IRB.

After approval by the PASC committee, storage Specimen Request Form (form 134) must be submitted to the lead analyst at the CC. This request from lays out the details needed in order to make the actual request to the storage lab (i.e., which cohort and visit) the amount and whether the specimen has been previously thawed. After submission of form #134, the same process used for formal data analysis requests will be followed. (see phase III, formal analysis and writing page # 2-7.)

Publication of Ancillary Study Results

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

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

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

"The authors are extraordinarily appreciative of the DASH-Sodium participants and of the entire DASH-Sodium Research Group, which included investigators and staff from the Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, MD; the Kaiser Permanente Center for Health Research, Portland, OR; Duke University Medical Center, Durham, NC; Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA; The Johns Hopkins Medical Institutions, Baltimore, MD, and Endocrine-Hypertension Division, Brigham & Women's Hospital, Boston, MA."

No abstracts from DASH2 ancillary studies that include post-randomization data may be submitted until the main outcomes abstract has been presented. Papers for DASH2 ancillary studies may not be submitted until the main outcome paper for DASH2 has been accepted for publication.

Availability and Analysis of Data

Prioritization

Requests for DASH2 data and their analyses can be submitted to the Coordinating Center after approval by the PASC. The Coordinating Center notifies the PASC if resource limitations do not permit a timely completion of an analysis request, in which case the PASC assigns priority rankings to projects so that the highest priority projects are completed first.

Release of Data for Public Access

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

Archiving of Source Documents and Biological Specimens

All source documents and biological specimens obtained during the conduct of DASH2 should be stored until the year 2007 or until the PASC formally dissolves. Before any source documents or biological specimens are discarded, approval must be sought from the Steering Committee. Before disbanding, the Steering Committee will determine the future storage or disposal of source documents and stored biological specimens.

Appendix 2.1 Authorship

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

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

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

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

Editors may require authors to justify the assignment of authorship.

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3. Human Subjects

To participate in DASH2, participants must provide written, informed consent using procedures reviewed and approved by each clinical center's local IRB. This consent should cover screening visits, run-in, and intervention. The number and timing of these consents are determined by the local IRBs and may vary across the clinical centers.

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

Summary descriptions of each clinical center's consent procedures are included as part of this chapter. In addition, the Coordinating Center maintains copies of each clinical center's consent documents.

Principles of Informed Consent

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

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

Process of Obtaining Informed Consent

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

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

Summary of Site-Specific Consent Procedures

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

Baltimore

At John Hopkins, consent forms will be obtained at up to four points in the DASH2 trial. At the first in-person visit, consent for blood pressure measurement will be obtained. If the person meets the basic PSV BP criteria, the participant will be asked to sign another consent form which covers the formal screening visits (SV1-SV3) and run-in period. At the end of run-in,

participants will be asked to sign a third consent form which covers randomization and the three feeding periods. The final consent form pertains to collection of DNA and will be obtained once during one of the three feeding periods.

Baton Rouge

Consent for DASH2 volunteers at the Pennington Biomedical Research Center is a two-stage process. For Screening Visit 1 (SV1) requirements, all participants are instructed in and sign a generic consent form agreeing to a battery of phlebotomy, body composition, blood pressure questionnaire, and other evaluations. These measures are conducted on subjects receiving evaluations for any study at the Pennington Center. For potential DASH2 participants, this screening is altered only in that the blood pressure determination is done with a random zero rather than a standard mercury manometer.

For those individuals who continue to qualify, all subsequent DASH2 screening visits, feeding, regimens, and other evaluations are conducted only after additional consent specific to the DASH2 study is obtained

Boston

Consent forms will be used for the screening visits and feeding phase of the study. Both consent forms will be reviewed and approved by the Brigham and Women's Hospital Human Research Committee. Study participants who are interested and eligible in participating in the screening phase of the study will be provided with the consent form to review and sign at the SV1 visit. This consent form will describe the procedures to be followed during the screening phase of the study. After completion of all screening visits and prior to feeding, study participants who are interested and eligible in continuing with the feeding phase of the study will be provided with a second consent form to review and sign. This consent form will describe the procedures to be followed in the feeding phase of the study. Study investigators will be available to review the study protocol and answer any questions study participants may have at both times that informed consent is obtained.

Durham

Participants will sign written informed consent, approved by the Duke University Committee for Clinical Investigation (IRB), at the first screening visit. This single consent form will cover all study activities for that particular participant. A copy will be kept on file, and a duplicate will be given to the participant.

Assurance of Informed Consent

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

Confidentiality

All participant information, and even the fact that an individual is participating in the study, is considered confidential. This confidentiality is assured in DASH2 through several mechanisms. First, each participant is assigned an anonymous study ID, which is then used on all study forms. Only where absolutely necessary to assure data integrity is a participant's name also included on study forms.

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

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

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

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

Data Integrity

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

Risks

The DASH2 study should not involve any major health risk to participants. The most likely physical health risks associated with participation are gastrointestinal upset (e.g., bloating), increased frequency and bulk of stools (resulting from the high fiber content of some diets), and minor discomfort from the venipunctures. These effects are either transient or readily reversible once off the study diets. The DASH experience suggests that GI discomfort, though common, is generally minor and appears to subside over time. Participants are monitored for reactions to the diets, and the diet can be terminated if necessary (although this was not necessary during the DASH study).

Depending on a participant's baseline diet, some of the dietary patterns and sodium levels under study may lead to slight, transient increases in blood pressure that are not sufficient to significantly raise risk for any morbid consequences. Nonetheless, the Protocol includes regular monitoring for adverse events during feeding, and all such events, whether or not related to the study, are documented and reported to the Data and Safety Monitoring Board (DSMB).

Participant blood pressure is monitored weekly during the feeding periods and potentially "at-risk" individuals, including those taking blood pressure medications, are excluded during screening. In addition, participants are referred for medical evaluation if their blood pressure exceeds pre-established "escape" levels, and are dropped from the study if they subsequently need to start on blood pressure medication. The Coordinating Center regularly reports to the DSMB on individuals who reach escape blood pressure levels.

Additional risks to study participants include: accidental breach of confidentiality; the inconvenience of having to come to the clinic each day to eat a meal and only being allowed to eat assigned study foods; the inconvenience of collecting 24-hour urine specimens; and the inconvenience of wearing an ABPM device.

Benefits

The benefits associated with participation in the study include: free food for approximately 15 weeks, regular blood pressure monitoring, cash reimbursement (amounts vary by center), and free laboratory tests that have a small possibility for early diagnosis of an illness. Participants also have the satisfaction of participating in a clinical trial with potentially major public health implications.

Based on the results of DASH, we anticipate that a majority of participants randomized to the combination dietary pattern will experience a reduction in blood pressure while on this diet. In addition, all participants will receive two months of food that is at or below current US

recommendations for sodium intake. Again based on the DASH experience, even the higher sodium level will be lower than what many participants normally consume. Changes in blood pressure associated with the DASH2 diets, however, whether up or down, are unlikely to be of any clinical significance over the relatively short duration of the study.

Gender and Minorities

The DASH2 study will recruit a population that is 50% African American and 50% female. Recruitment of minorities and women is formally monitored quarterly and reports forwarded to NHLBI. Minorities other than Blacks are also eligible to participate, although no targets are set for this category and they will be grouped with White participants for analysis. All of the participating centers have demonstrated in DASH their ability to recruit large numbers of African Americans and women. Further, we have specifically powered the study to have good power to detect sodium effects for race and gender subgroups.

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Summary of Edits

New changes in version 1.1

- Changes to the required time off certain medications prior to participation

4. Recruitment

Study Population

The study sample consists of approximately 400 healthy, free-living adult men and women, age 22 years and older, who have a SBP of 120-159 mm Hg and a DBP of 80-95 mm Hg . Given the disproportionate burden of hypertension and its complications among African Americans, as well as their potential for differential salt sensitivity, one-half of DASH2 participants are of African American background. We also include equal numbers of men and women and 30 percent hypertensives in order to examine the issue of salt sensitivity separately for these subgroups as well. The unequal split between hypertensives and nonhypertensives reflects the strong evidence in the literature that the effects of salt sensitivity are more pronounced in hypertensives than in nonhypertensives.

Eligibility Criteria

To be eligible to participate in DASH2, participants must meet a number of eligibility requirements (table 4-1). These eligibility requirements were selected to exclude individuals with conditions, special dietary requirements, or taking medications, that would affect blood pressure or micronutrient metabolism and individuals with potentially serious chronic health conditions.

The DASH2 eligibility criteria are assessed during the course of several screening visits and during a period of run-in feeding prior to randomization. This section lists the various eligibility requirements and gives the operational criteria by which they are determined. Because of the potentially long lag between the initial screening visit and the start of run-in, the Protocol stipulates that key medical eligibility criteria, if initially determined more than one month prior to the start of run-in, must be confirmed within this timeframe. The trial's data entry application checks to make sure this is the case.

Several of the eligibility criteria relate to laboratory tests conducted using blood or urine specimens. Any initially abnormal laboratory values that would result in exclusion may, at the discretion of the local Principal Investigator (PI), be repeated once and the participant retained if the second value falls within eligible limits. Exceptions to this rule are for elevated blood sugar and hyperlipidemia. Repeat testing for these conditions requires an alternative measure to that used for the initial assessment. All laboratory assessments for eligibility are performed locally, and, unless specifically noted otherwise, eligibility is based on local normal ranges.

Table 4-1. DASH2 Eligibility Criteria

Inclusion Criteria

- —SBP120-159 mm Hg and DBP 80-95 mm Hg based on mean values over three screening visits
- —Age ≥22 years
- —Willing to eat at least one on-site meal/day, five days/week, and willing to eat study diets and nothing else for the 14 weeks of controlled feeding
- —Willing and able to provide informed consent

Exclusion Criteria

Medical Conditions:

- —Any serious illness not otherwise specified that would interfere with participation
- —Currently on cancer chemotherapy or with evidence of active malignancy or radiation therapy within past six months
- —Hematocrit at least 5 percentage points below local laboratory's gender-specific normal range (unless PI has reason to believe this is not due to nutritional deficiency)
- — History of CVD event (MI, CABG, angioplasty, symptomatic ischemic heart disease, or stroke)
- —Clinical diagnosis of congestive heart failure
- —Inflammatory bowel disease, colostomy, malabsorption, or any prior GI resections other than localized colonic resections
- —serum transaminase > 2 times the local laboratory's upper range of normal, or a clinical diagnosis of hepatitis as determined locally
- —ED visit or hospital stay for asthma or COPD in last six months, or other evidence of recent instability in asthma or COPD
- —Renal insufficiency as determined by both an elevated serum creatinine level (> 1.2 mg/dL for women or > 1.5 mg/dL for men) and a glomerular filtration rate < 60 ml/min as estimated using the Cockrault-Gault formula
- —Hypo- or hypercalcemia (serum Ca >0.3 mg/dL above or below local laboratory normal range)
- —Hypo- or hyperkalemia (serum K >0.2 mg/dL above or below local laboratory normal range)
- —Urine dipstick protein ≥2+
- —Random glucose ≥180 mg/dL or positive urine dipstick for glucose; repeat testing may include fasting blood sugar (FBS) or HgbA1C. For FBS, exclude if ≥140 mg/dL. For HgbA1C, exclude if ≥8 (or local lab equivalent to an average blood sugar ≥200 mg/dL)
- —Body mass index > 40 Kg/m^2
- —DASH2 staff or household member of DASH2 staff

Medications:

—Use of blood-pressure-lowering drugs within the three months prior to randomization and the one month prior to SV1
—lithium
—insulin
—oral corticosteroids
—unstable doses of psychotropics or phenothiazines
—cholestyramine
—colestipol
—unstable doses of statins or other lipid-lowering agents not already excluded
—oral breathing medications
—dilantin
—antacids containing magnesium or calcium, unless they can be discontinued
—digitalis
—weight-reducing medications
— OTC medications or other consumer products providing 3 or more mmol of sodium per serving, unless they can be discontinued

Other Exclusionary Criteria:

—Given the trial's CVD exclusions, hyperlipidemia is less of a health concern than it was in DASH. Exclude if total cholesterol >260 mg/dL. Repeat testing based on LDL (determined either directly from a nonfasting blood sample or computed from a fasting blood sample). If this would require pharmacotherapy according to NCEP guidelines, then exclude. The NCEP guidelines to initiate pharmacotherapy for LDL cholesterol are:

- $\geq$ 220 mg/dL for young adults (men under 35 and premenopausal women) without 2+ CVD risk factors,
- $\geq$ 190 mg/dL for older individuals without 2+ CVD risk factors, and
- $\geq$ 160 mg/dL for individuals with 2+ CVD risk factors.

(See Appendix 4.1 for guidelines on determining lipid eligibility.)

—Consumption of more than 14 alcoholic drinks per week
—Investigator discretion for safety or compliance reasons
—Inability to provide reliable blood pressure measurements
—Current use of vitamin or mineral supplements or salt substitutes that cannot be stopped
—Use of chewing tobacco, snuff, or other smokeless tobacco products
—Planning to leave the area prior to the anticipated end of the intervention period
—Pregnant, planning a pregnancy prior to the end of intervention, or breast feeding
—Significant food allergies, preferences, or dietary requirements that would interfere with diet adherence

Inclusion Criteria

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

Two blood pressure measurements are taken at each of the first three formal screening visits (SV1, SV2, and SV3), and the average of these six measurements must fall within the stated limits for both SBP and DBP. In order to identify participants not likely to meet these limits, somewhat wider eligibility limits are also established for the average cumulative blood pressures at each of SV1 and SV2 (see MOP Chapters 6 and 7).

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

- Age > 22 years

Participants must be 22 years of age or older at start of run-in feeding.

Operationally, this is assessed by asking, at the prescreening visit, whether the participant is currently 22 years of age or older. Date of birth is also collected for confirmation.

- Willing to eat at least one on site meal/day, five days/week, and willing to eat study diets and nothing else for 14 weeks

The nutrition staff repeatedly stress this issue with potential participants, and the run-in feeding period is a further test of the participant's willingness to comply with the trial's strict eating requirements.

- Willing to provide written informed consent

In order to participate in the study, all subjects must provide written, informed consent using procedures that are reviewed and approved by each center's local IRB.

Exclusion Criteria

- Currently on cancer chemotherapy or with evidence of active malignancy or radiation therapy within past six months

The diagnosis of cancer and the status of therapy are based on the participant's self-report and do not need to be confirmed with the participant's physician unless a question exists about whether the cancer is currently active.

- Anemia

Defined as a hematocrit at least 5 percentage points below the local laboratory's gender-specific normal range (unless PI has reason to believe this is not due to nutritional deficiency).

- Cardiovascular disease or congestive heart failure

Participants are excluded if they report a prior CVD event (defined as stroke, MI, heart failure, CABG, hospitalization for unstable angina, or coronary angioplasty) or if they report a clinical diagnosis of congestive heart failure. Confirmation is not necessary unless the participant is uncertain of the diagnosis and the clinical center still wishes to include him/her.

- Inflammatory bowel disease, colostomy, malabsorption, or any prior GI resections other than localized colonic resections

Defined based on self-report. Confirmation is not necessary unless the participant is unsure of the diagnosis and the clinical center still wishes to include him/her.

- Hepatitis

Defined as a serum transaminase level more than 2 times the local laboratory's upper range of normal, or a clinical diagnosis of hepatitis as determined locally.

- Unstable asthma or COPD

Defined as an emergency department visit or hospital stay for asthma or COPD in last six months, or other evidence of recent instability in asthma or COPD. Health care utilization is based on participant self-report and need not be confirmed. "Other evidence of recent instability" must be determined by the local PI based on information provided by the participant.

- Renal insufficiency

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

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

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

- Hypo- or hypercalcemia

Defined as a serum calcium level more than 0.3 mg/dL above or below local laboratory's normal range.

- Hypo- or hyperkalemia

Defined as a serum potassium level more than 0.2 mg/dL above or below local laboratory's normal range.

- Urinary protein

Defined as a urine dipstick protein level greater than or equal to "2+".

- Non insulin-dependent diabetes

Defined as either a nonfasting random glucose $\geq$ 180 mg/dL or a positive urine dipstick for glucose. Repeat testing to confirm the diagnosis may include either a fasting blood sugar (FBS) determination or measurement of HgbA1C. For FBS, the participant is still excluded if the blood sugar level is $\geq$ 140 mg/dL. For HgbA1C, the participant is still excluded if the level is greater than or equal to eight (or whatever is the local lab equivalent to an average blood sugar at least 200 mg/dL).

- Hypercholesterolemia

Defined as a serum cholesterol level > 260 mg/dL. Repeat testing may include either fasting cholesterol, fasting indirect LDL or non-fasting direct LDL. Exclude if fasting cholesterol is >260 mg/dL or if LDL level would trigger pharmacotherapy according to NCEP guidelines. (See Appendix 4.1.) If fasting cholesterol is $\leq$ 260 mg/dL, subject is eligible regardless of LDL (i.e., if both appear on the lab results).

- Any serious illness not otherwise specified that would interfere with participation

Based on self-report. Final determination of whether an illness would preclude participation is left to the local clinical center.

- Specific medication use

In addition to having any of the medical conditions listed in Table 4.1, participants are also excluded from participation if they report taking any of the following medications. Unless noted otherwise, **current medication use is defined as any use within 21 days of the PSV visit or at any time thereafter**. All participants are expected to bring their medication bottles to the SV2 visit for review by a clinic staff member.

- use of blood-pressure-lowering drugs within the three months prior to randomization and the one month prior to SV1
- lithium
- insulin
- oral corticosteroids

- cholestyramine
- colestipol
- oral breathing medications (i.e., for asthma and/or COPD)
- dilantin
- antacids containing magnesium, or calcium, unless they can be discontinued (see Appendix 4.5 for allowed antacids)
- digitalis
- weight reducing medications (see Appendix 4.3)
- OTC medications or other consumer products providing 3 or more mmol of sodium per serving or otherwise able to interfere with nutrient intake, unless they can be discontinued (see Appendix 4.5 for allowed cold and allergy medications)
- certain cold and allergy medications, unless they can be discontinued (see Appendix 4.2)
- unstable doses of statins or other lipid-lowering agents not already excluded (see Appendix 4.4) ("Unstable doses" of these medications are operationally defined by the participant having either started, stopped, or changed the dosage of these medications during the four weeks prior to SV1)
- unstable doses of psychotropics or phenothiazines ("Unstable doses" of these medications are operationally defined by the participant having either started, stopped, or changed the dosage of these medications during the past six months)

In addition to the above medications that are <u>not</u> allowed, Appendix 4.5 lists other medications that <u>are</u> approved for treatment of constipation, indigestion, and other minor conditions.

- Consumption of more than 14 alcoholic drinks per week

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

- Body mass index greater than 40 Kg/m^2

Operationally this is determined in two stages. At the PSV, each participant is asked to give his weight and height. Since height is typically reported with a good degree of accuracy and weight is usually underreported, anyone whose self-reported BMI exceeds 40 Kg/m^2 is excluded. In addition, weight and height are formally measured at either SV1, or SV2 and, if the BMI computed using these measurements exceeds 40 Kg/m^2, the participant is also excluded.

- Poor compliance during screening and/or run-in

At any time prior to randomization, each clinical center has the option of excluding participants for noncompliance with the study protocol. Noncompliance may include, for example, repeated no-shows or reschedules for clinic visits, poor attitude, or any other aspect of the participant's behavior that would suggest he/she is a poor candidate for the trial.

In addition, each participant's eating record is reviewed by the clinic staff just prior to randomization in order to assess compliance with the feeding protocol. Participants who do not comply with the demands of the feeding protocol are excluded at this time. A more detailed discussion of dietary compliance is given in the Diet MOP.

- Investigator discretion for reasons of safety

In addition to the trial's mandatory blood pressure escape levels, individual centers always have the option of excluding participants for reasons of safety as determined locally.

- Unwilling or unable to modify current diet

A necessary prerequisite for participation in the study is a willingness and ability to comply with the study's strict eating guidelines. In particular, participants with significant food allergies, preferences, or dietary requirements that would interfere with dietary adherence are excluded from participating.

Since this criterion, along with the blood pressure limits, is likely to account for the majority of study exclusions, it is imperative that participants understand the nature and demands of the study as early into the screening process as possible. The Protocol therefore builds in several levels of review with the participant during screening as well as a run-in feeding period prior to randomization.

- Current use of food supplements that cannot or will not be stopped

- Current use of chewing tobacco, snuff, or other smokeless tobacco products

- Inability to provide reliable blood pressure measurements

As detailed in MOP Chapter 11, individuals for whom valid and reliable measurements of blood pressure cannot be obtained are excluded from participation in the trial. This criterion applies only to blood pressure measurements taken with a random zero sphygmomanometer, and not to those taken with an ambulatory blood pressure monitor. Individuals for whom the former measurements can be obtained, but the latter cannot, are allowed to participate.

- Planning to leave the area prior to the anticipated end of the intervention period

- Pregnant or planning to conceive prior to the anticipated end of intervention (women only)

Operationally any woman who is pregnant or trying to conceive a child at the time of the prescreening visit is excluded from the study.

- Breast feeding

Women who are actively breast feeding at the time of the prescreening visit are excluded from the study.

- DASH2 staff or household member of DASH2 staff

Overview of Recruitment

Each DASH2 clinical center recruits its participants in four separate feeding cohorts. Specific recruitment approaches include 1) targeted mailings to specific groups (e.g., employees of local industries, previous screenees), 2) mass mailings (e.g., vis-à-vis inserts in coupon packs and brochures to registered voters or licensed drivers), 3) community and worksite screenings, 4) and mass media advertising (e.g., radio and television advertisements and public service announcements).

Recruitment efforts at each site are broad-based. Although previous DASH participants are not excluded from participation in DASH2, recruitment is not focused on these individuals, and the number who do enroll in DASH2 is monitored.

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

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

Record Keeping

Other than for basic demographic information (e.g., gender and race), data collected at PSV are not considered study data and are not incorporated into the study database. The demographic data are entered only for participants who are eligible to continue on to SV1. Individual clinical centers wishing to enter demographic data on all participants can do so, and the data management system will permit site-specific reports of this data for recruitment tracking purposes.

Beginning with SV1, all data collected on prospective participants must be entered into the data management system, and all subjects who drop out of screening, become ineligible, or who are otherwise lost to follow-up must be formally closed out.

Appendix 4.1 Guidelines for Determining Lipid Eligibility

1. If total cholesterol ≤260 then **ELIGIBLE.** Otherwise, you have the option of obtaining an LDL and continuing with Step 2.

2. If LDL<=160 then **ELIGIBLE**. Otherwise go to Step 3

3. LDL>220 then **INELIGIBLE**. Otherwise go to Step 4

Males	**Females**
4. If age>35 and LDL>190 then **INELIGIBLE**. Otherwise go to Step 5	**4.** If post-menopausal and LDL>190 then **INELIGIBLE**. Otherwise go to Step 5
5. Calculate risk factors: ☐ ≥45 years old ☐ Family hx of CHD (MI or sudden death in a first-degree male relative <55 or a female <65) ☐ Current smoker ☐ BP >140/90 mm Hg ☐ HDL <35 mg/dl ☐ Diabetes mellitus TOTAL RISK FACTORS: _____ Negative risk factor: If HDL ≥ 60 mg/dl then subtract 1 from positive risk factors to get: TOTAL RISK FACTORS: _____ If TOTAL is 2+, then participant is **INELIGIBLE.** Otherwise participant is **ELIGIBLE.**	**5.** Calculate risk factors: ☐ ≥55 years old and no estrogen replacement ☐ Not menstruating and no estrogen replacement ☐ Family hx of CHD (MI or sudden death in a first-degree male relative <55 or a female <65) ☐ Current smoker ☐ BP >140/90 mm Hg ☐ HDL <35 mg/dl ☐ Diabetes mellitus TOTAL RISK FACTORS: _____ Negative risk factor: If HDL ≥ 60 mg/dl then subtract 1 from positive risk factors to get: TOTAL RISK FACTORS: _____ If TOTAL is 2+, then participant is **INELIGIBLE.** Otherwise participant is **ELIGIBLE.**

Appendix 4.2 Over-the-Counter Drugs and Products Not Allowed in DASH2

Metamucil
Rolaids
Tums

Sodium-containing drugs / products

Baking soda toothpaste
Baking soda for upset stomach
Alka Seltzer
Bisodol powder
Bromo-seltzer
Chewing tobacco

Appendix 4.3 Exclusionary Weight-Loss Drugs

Generic name	Brand name
benzphetamine	Didrex
dexfenfluramine	Redux
diethylpropion	Tenuate Tepanil
fenfluramine	Pondimin
phentermine	Adipex Fastin Ionamin Obenix Oby-Cap Oby-Trim Pro-Fast Zantril
fenfluramine/phentermine	Fen/Phen
mazindol	Sanorex Mazanor
phendimetrazine	Plegine X-trozine Bontril Prelu-2
phenmetrazine	Preludin
phenylpropanolamine	Dexatrim Accutrim
d-amphetamine	Dexadrine Dextrostat
methamphetamine	Desoxyn
orlistat	Xenical
sibutramine	Meridia

Appendix 4.4 Lipid-Lowering Drugs That Are Exclusionary Only if the Dosage Is Unstable

Generic name	**Brand name**
lovostatin	Mevacor
pravastatin	Pravachol
simvastatin	Zocor
fluvastatin	Lescol
atorvastatin	Lipitor
nicotinic acid	Niacin Slo-Niacin Niacor Nicobid Niacinamide Nicotinamide
gemfibrozil	Lopid
clofibrate	Atromid-S
bizafibrate	Bezalip
dextrothyroxine sodium	Choloxin
probucol	Lorelco

Appendix 4.5 Medications ALLOWED during DASH2

Medical condition or symptom	
Aches and pains	Tylenol Aspirin Ibuprofen (but not within 48 hours before BP measurement)
Indigestion	Amphogel Nephrox
Cold/flu/allergy	Tylenol, Extra Strength Tylenol Chlortrimeton Benadryl Hismanal Seldane Tavist Afrin, Otrivin or Ayr nasal spray Robitussin (NOT Robitussin DM) Claritin Beconase nasal spray
Constipation	Correctol Senokot
Infections	Antibiotics
Hormones	Estrogen and progesterone (but don't start these meds or change dose during the study)

If you want to take any other medication, you must first discuss it with DASH2 study personnel. Many medications can interfere with the DASH2 study, so please ask first!

5. PRESCREENING VISIT (PSV) 3

Overview 3

Setting 3

Preparations for Prescreening Visit 3

Conducting the Prescreening Visit 4

Procedures for Conducting the Visit by Phone 4
- Greet the Participant 4
- Describe the Study and Administer Prescreen Eligibility Form 4
- Ending the Prescreening Visit 5

Procedures for Conducting the Visit in Person 6
- Describe the Study and Administer Prescreen Eligibility Form 6
- Assess Blood Pressure (Optional) 7
- Ending the Prescreening Visit 7

Summary of Edits

5. Prescreening Visit (PSV)

Overview

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

The PSV is intended as a fast, efficient way to identify ineligible participants. The visit includes questionnaire data for exclusion and a single, optional, non-RZ blood pressure measurement. Individuals who complete the PSV are either excluded from further participation or scheduled for screening visit #1 (SV1), which may occur concurrently with the PSV.

If more than 120 days elapse between the PSV and SV1, the PSV must be repeated.

Setting

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

Preparations for Prescreening Visit

The following materials are needed to conduct the prescreening visit:

- Standard (non-RZ) sphygmomanometer and stethoscope (optional)
- PSV reference chart (included at back of chapter)
- Informed consent form for PSV (if required by local IRB, see Chapter 3)
- DASH2 Fact Sheet (included at back of chapter)
- Prescreen Eligibility Form (Form #01)

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

If SV1 is to be held in conjunction with the PSV, additional forms and equipment are also needed (see Chapter 6 for details).

Conducting the Prescreening Visit

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

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

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

Procedures for Conducting the Visit by Phone

At most sites, the initial direct contact between participants and clinic staff will most often be by telephone. Potential participants will usually be responding either to a direct mailing, radio advertisement, or some other recruitment effort. The level of knowledge about the study will vary greatly among respondents depending on the manner in which the participant heard about the study. For example, if the participant has received a copy of the DASH2 brochure, she may already be aware of some of the study's feeding requirements and is likely to satisfy many of the PSV eligibility requirements.

Greet the Participant

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

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

The participant will then identify herself and ask to speak with someone about the study. Participants may either identify the study by name or they may refer to it as the "eating study" or use other similar language. Be sure that whoever answers the phones, if the line is used for more than one study, is familiar enough with the study and the recruitment materials to be able to properly refer the participant to a DASH2 staff member.

Describe the Study and Administer Prescreen Eligibility Form

The DASH2 staff member should quickly confirm that the participant is calling about participating in the study, provide a brief overview, and begin to administer the Prescreen Eligibility Form. For example,

"That's right, the name of the study is the Dietary Approaches To Stop Hypertension 2 study, or DASH2 for short. Let me tell you a little bit about the study, and then if you are still interested I have a few quick questions to ask you to see if you might be eligible to participate."

[Review DASH2 Fact Sheet with participant. A copy is included at the end of this chapter.]

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

If No,

"Well, thanks for your interest anyway."

If Yes,

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

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

Ending the Prescreening Visit

If, after completing the Prescreen Eligibility Form, the participant is ineligible, thank her for her time and interest and conclude the conversation. The Prescreen Eligibility Form does not need to be entered into the data entry/management system unless the site chooses to do that for their own tracking purposes.

If the participant is eligible, complete fields 15-23 on the form. Schedule a date for the SV1 visit, thank the participant for his interest in the study, and terminate the conversation.

The Prescreen Eligibility forms will be collected and entered by the data entry person on site. At this time the data entry/management application will assign a study ID# which will be recorded on the Prescreen Eligibility Form. After entry of the Prescreen Eligibility forms, the data entry person or the clinic coordinator can print out labels from the data entry/management application for all participants who were eligible to continue.

Participant IDs are assigned using the following algorithm: The first three letters of the participant's last name, followed by the first two letters of the first name, followed by a one-digit site ID number, followed by a four-digit random number. If the last name or first name has fewer characters than needed to use this algorithm, an asterick will be used as a placeholder. For example, if the participant's name is Sue Wu, the first five characters of the ID will be WU*SU. When entering data or looking up data in the data entry/management application, the clinic

coordinator will need to include the asterisk in the participant's ID. (See Data Entry/Data Management User's Manual for further information on ID numbers.)

Procedures for Conducting the Visit in Person

In some cases, such as health fairs, the initial contact with the participant will be in person. Depending on the format of these screenings, the participants may or may not have heard about the study when they meet the study staff person. For example, they may simply think they are waiting for a free blood pressure screening, or they may have been given a copy of the DASH2 brochure to read while they are waiting in line. If blood pressure is measured as the first part of the visit and the participant is ineligible (see guidelines below), the Prescreen Eligibility Form need not be completed.

Describe the Study and Administer Prescreen Eligibility Form

Whenever it makes sense to do so in the context of the screening, the DASH2 staff member should introduce herself as part of the study, provide a brief overview of the study, and begin to administer the Prescreen Eligibility Form. For example,

> "Your blood pressure is xxx over xxx, which is in the high end of the normal range, and as a result you might be eligible to participate in a study we are doing to help people reduce their blood pressure by changing what they eat. The name of the study is the Dietary Approaches To Stop Hypertension Study2, or DASH2 for short. Let me tell you a little bit about the study, and then, if you are still interested, I have a few quick questions to ask you to see if you might still be eligible to participate."
>
> [Review DASH2 Fact Sheet with participant. A copy is included at the back of the chapter.]
>
> "Does the study sound like something you might be interested in?"

If No,

> "Well, thanks for your interest anyway."

If Yes,

> "Great. What I'd like to do then is to ask you a few questions and, if you are still eligible, schedule you for a clinic visit. Are you ready?"
>
> Begin administering the Prescreen Eligibility Form, the instructions for which may be found in the Forms Manual. At any point that it becomes evident that the participant is not eligible, you can terminate the visit.

Assess Blood Pressure (Optional)

Most likely the blood pressure assessment will occur as the first stage of these visits, though in some cases it may occur after the Prescreen Eligibility Form has been administered. The PSV blood pressure assessment consists of a single, non-RZ blood pressure measurement conducted in a seated position. No eligibility limits are established for the PSV blood pressure measurement. It is recommended, however, that individuals with a DBP less than 76 mm Hg or and SBP less than 116 be excluded. Individual clinics should establish their own upper eligibility limits, and participants whose blood pressure exceeds these limits should be excluded and referred to a physician for further follow-up.

Ending the Prescreening Visit

If, after concluding the visit, the participant is ineligible, thank him for his time and interest and conclude the conversation. The Prescreen Eligibility Form does not need to be entered into the data entry/management system unless the site chooses to do that for their own tracking purposes.

If the participant is eligible, complete fields 15-23 on the Prescreen Eligibility Form and schedule an SV1 visit. Thank the participant for his interest in the study and terminate the conversation.

The Prescreen Eligibility forms will be collected and entered by the data entry person on site. At this time the data entry/management application will assign a study ID# which will be recorded on the Prescreen Eligibility Form. After entry of the Prescreen Eligibility forms, the data entry person or the clinic coordinator can print out labels from the data entry/management application for all participants who were eligible to continue.

PSV Reference Chart

Body Mass Index Table (for use with Prescreen Eligibility Form)

Locate participant's height (from Q13) on the table below and note the accompanying threshold weight. If participant's weight (from Q14) equals or exceeds this threshold, the participant is ineligible based on BMI.

threshold height	threshold weight	threshold height	threshold weight	threshold height	threshold weight
4'6"	165.9	5'5"	240.4	6'4"	328.6
4'7"	172.1	5'6"	247.8	6'5"	337.3
4'8"	178.4	5'7"	255.4	6'6"	346.1
4'9"	184.8	5'8"	263.1	6'7"	355.1
4'10"	191.4	5'9"	270.9	6'8"	364.1
4'11"	198.0	5'10"	278.8	6'9"	373.3
5'	204.8	5'11"	286.8	6'10"	382.5
5'1"	211.7	6'	294.9	6'11"	391.9
5'2"	218.7	6'1"	303.2	7'	401.4
5'3"	225.8	6'2"	311.5		
5'4"	233.0	6'3"	320.0		

Dietary Approaches to Stop Hypertension (DASH2) Study

DASH2 FACT SHEET

Please use the following "script" to describe the key features of the study as a part of PSV screening. This will help ensure that all participants have a common knowledge base about the study.

- Purpose of the DASH2 Study is to find out if eating foods rich in certain nutrients and varied amounts of salt will reduce BP.
- Provide all meals for 14-15 weeks.
- Must be available to come to (name of facility) every M-F for a meal (lunch or dinner).
- Food for the other two meals/day plus snacks and weekend meals will be provided to "Take-Home."
- Must eat only study food for the 14-15 weeks (participants will be randomized to one of two diets).
- NOT a weight-loss study; weight is monitored and amount of food provided is adjusted to make sure that weight does not change during study.
- BP monitoring at least weekly; three times during study, participants will wear a 24-hour ambulatory BP monitor.
- Four to five blood tests required (once or twice during screening and three times during 14-week feeding).
- Four 24-hour urine collections required (once or twice during screening and three times during 14-week feeding period).
- There will be a process of three screening visits (each visit at least one week apart) in which the prospective participant must qualify (all three visits) before eligible to participate in study.
- At the completion of participation in the study, participant will receive $xxx.

6. SCREENING VISIT 1 (SV1) 3

Purpose 3

Setting 3

Preparations for SV1 Visit 3

Conducting the SV1 Visit 4

Confirm participant ID and check for completed PSV 4
Review the study and confirm participant interest 5
Assess blood pressure 5
Measure participant's weight and height and check BMI (optional) 5
General Dietary Information Questionnaire (Form #100) 5
Eligibility Questionnaire (Form #06) 6
Participant Information Sheet 6
SV1 Visit Form 6

Ending SV1 7

Summary of Edits

6. Screening Visit 1 (SV1)

Purpose

The purpose of SV1 is to continue screening prospective participants for eligibility based on blood pressure and their responses to the General Dietary Information Questionnaire. Participants will also be instructed on how to fill out the Eligibility Questionnaire. The initial SV1 may occur at any time, including the day of the PSV. However, if the SV1 occurs more than 120 days after the PSV, the PSV data are invalid and must be recollected prior to obtaining SV1 data. If a participant is excluded on or after SV1, that individual cannot be rescreened for the same cohort. The participant may, however, be rescreened for later cohorts.

Setting

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

If the SV1 visit is conducted at the same time as the PSV visit, the DASH2 staff person should leave the room at the end of the PSV visit and ask the participant to sit quietly for five minutes with his legs uncrossed. The SV1 visit is then conducted.

Preparations for SV1 Visit

The following materials are needed to conduct the SV1.

- Random zero (RZ) sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- Stadiometer
- Scale
- Consent materials (if required by local IRB; see Chapter 3)
- SV1 Blood Pressure Form (Form #02)
- Eligibility Questionnaire (Form #06)
- General Dietary Information Questionnaire (Form #100)
- SV1 Visit Form (Form #03)
- Study charts for scheduled participants (if available)
- Participant Information Sheet (Form #29)
- BMI Reference Chart

- Participant Closeout Form (Form #18)

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

- Prescreen Eligibility Form (Form # 01)

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

Conducting the SV1 Visit

SV1 activities are listed below. If required, obtain consent first. Whether consent is required or not, briefly redescribe DASH2 and obtain the participant's assurance that they are interested in participating. In general, blood pressure should be done before the other procedures because the forms need not be administered if the individual is not blood pressure eligible.

- Confirm participant ID
- Briefly redescribe the study; ask participant if they think they are interested in participating
- Obtain consent (if required by local procedures)
- Take two RZ blood pressure readings, complete the SV1 Blood Pressure Form, and note eligibility on SV1 Visit Form
- Have participant fill out the General Dietary Information Questionnaire and note eligibility on SV1 Visit Form
- Instruct participant in how to complete the Eligibility Questionnaire
- Record events and final eligibility status on the SV1 Visit Form
- Optional: Weigh participant, measure height, and check BMI (record on SV1 visit form)

Confirm participant ID and check for completed PSV

If participants completed a PSV on an earlier day, they will have been issued a study ID and have labels prepared for the SV1. If the SV1 is being completed at the same time as the PSV it is critical to put the participant's name on each page of each form completed and keep the stack together. The data entry person enters the forms, receives a study ID for the participant from the data entry/management application, and places that ID number on all completed forms.

If the person has been screened before but no study ID exists and a hard copy of the Prescreen Eligibility Form is not available, a new one must be done before the visit can proceed. In this case any old versions of the Prescreen Eligibility Form, if subsequently found, should be discarded.

The SV1 visit must occur within 120 days of the PSV visit. If this is not the case, then the PSV must be repeated. This holds even if the data from the prior visit have been entered into the computer. In this latter case the computer will generate a new study ID for the participant.

Review the study and confirm participant interest
(and obtain formal consent if required here by local procedure)

Briefly describe DASH2 again, emphasizing the commitment required of participants. Ask if the individual thinks he would like to participate if eligible. Tell the participant that it is very important that those who participate follow through and complete the study. Of course, anyone has the right to drop out whenever they wish, but they should also understand that too many dropouts will invalidate the study.

Assess blood pressure

After expressing continued interest (and providing formal consent if required), take the participant's blood pressure using the RZ device and the procedures described in Chapter 11 of the MOP (Blood Pressure Assessment). If the average of two systolic blood pressures is between 118 and 170 mm Hg and the average of the two diastolic pressures is between 78 and 100 mm Hg, the participant is eligible to continue to SV2.

N.B. cuff size must be appropriate. If it is impossible to get an accurate measurement (e.g., if large cuff covers the antecubital fossa or arm circumference is >52 cm.) the participant is excluded. (See Chapters 4 and 11.)

Participants who are excluded based on blood pressure readings above the allowable limits may need to be referred to a physician for further evaluation. If the average of the SBP measurements is >180 mmHg or the average of the DBP measurements is > 110 mmHg, the participant must be referred to a physician. The participant may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment even if the BP is lower than the above limits. If escape levels are reached or the participant is referred for BP management for some other reason, a BP escape tracking from should be filled out and one copy put in the participant chart at the site and one copy sent to the CC.

Measure participant's weight and height and check BMI (optional)

The participant's weight and height measurement may be collected at SV1 or SV2, as long as it is completed by SV2. Measure the participant's weight and height per the protocol outlined in MOP Chapter 13. Note the eligibility status on the SV1 Visit Form. Refer to the SV1 Reference Chart (located in the back of this chapter) to determine if the participant is BMI eligible.

General Dietary Information Questionnaire (Form #100)

The General Dietary Information Questionnaire is a short form designed to identify people who have food allergies or medical conditions that limit the types of foods they can consume and thus could interfere with their participation in DASH2. Have the participant complete this form. If there are questions about specific items, discuss them with the participant. Persons who cannot consume the food items listed on the form are not eligible to participate.

Eligibility Questionnaire (Form #06)

The Eligibility Questionnaire is designed to identify persons who are ineligible for medical or behavioral reasons. Remove the last page ("office use only" section) from the form, store it in the participant's study chart, and give the rest of the form to the participant to take home and return at the SV2 clinic visit. This form may also be administered as a part of the SV1 visit. If the participant is not eligible for SV2, he should not receive this form. Be sure to place a label with the participant's study ID on each page of the form. If an ID has not yet been assigned, write the participant's name on each page of the form.

The instructions for completing the questionnaire should be discussed with the participant at this time. Ask participants that when they have questions or are unsure about an item to check "unsure" and write a comment or question in the comment section for that item and ask about it at the SV2 visit. Staff should discuss these items with participants at SV2.

The questionnaire asks participants to indicate whether or not they are taking various medicines or over-the-counter products, including vitamins and other supplements. Ask participants to check their medication bottles for the names of their medications. In addition, instruct participants to bring to the SV2 visit all medications and over-the-counter products (including vitamins, supplements, and other non-prescription drugs) that they regularly take. A DASH2 staff person will list these medications in the "office use only" section of the Eligibility Questionnaire at the SV2 visit.

Participant Information Sheet

Fill out a Participant Information Sheet (Form #29) on each participant to file in the participant chart.

SV1 Visit Form

After each portion of the visit is completed, a DASH2 staff person should check the appropriate "Done?" box on the SV1 Visit Form and (if applicable) indicate whether the participant is eligible or not eligible to continue based on that portion of the visit. At the end of the visit a staff person should review this form to make sure that the participant has completed all of the necessary components. This person should also make sure that a single outcome status is coded at the bottom of the form and should enter their ID in the "Reviewed by staff ID" field.

If a participant is excluded at the investigator's discretion (i.e., not as part of the regular screening activities for that visit), check "ineligible" under the Visit Outcome section of the SV1 Visit Form and in addition complete the Participant Closeout Form (Form #18) to record the reason for the exclusion.

Ending SV1

To complete the SV1 visit, do the following:

- Inform the participant of eligibility status. You may inform the participant of eligibility status and terminate the visit whenever it is clear that the individual is not eligible for DASH2. Explain the reasons for ineligibility to participant. Enter the visit outcome status onto the SV1 Visit Form.
- If participant is eligible, schedule an appointment for SV2 at least seven days from SV1. Enter the SV1 Visit Form and SV1 Blood Pressure form into the data entry/management system. This should be done within one week of the visit.

BMI Reference Chart

Body Mass Index Exclusion Cutpoints

Locate participant's height on the table below and note the accompanying maximum weight. If participant's weight equals or exceeds this value, the participant is ineligible based on BMI.

Height (cm)	Maximum weight (Kg)	Height (cm)	Maximum weight (Kg)
139	77.2	176	123.9
140	78.4	177	125.3
141	79.5	178	126.7
142	80.6	179	128.2
143	81.7	180	129.6
144	82.9	181	131.0
145	84.1	182	132.5
146	85.2	183	134.0
147	86.4	184	135.4
148	87.6	185	136.9
149	88.8	186	138.4
150	90.0	187	139.9
151	91.2	188	141.4
152	92.4	189	142.9
153	93.6	190	144.4
154	94.8	191	145.9
155	96.1	192	147.5
156	97.3	193	149.0
157	98.5	194	150.5
158	99.8	195	152.1
159	101.1	196	153.7
160	102.4	197	155.2
161	103.6	198	156.8
162	104.9	199	158.4
163	106.2	200	160.0
164	107.5	201	161.6
165	108.9	202	163.2
166	110.2	203	164.8
167	111.5	204	166.5
168	112.8	205	168.1
169	114.2	206	169.7
170	115.6	207	171.4
171	116.9	208	173.1
172	118.3	209	174.4
173	119.7	210	176.4
174	121.1	211	178.1
175	122.5	212	179.8
		213	181.5
		214	183.2

BMI=weight/ht^2 (Kg/m^2)---exclude if >40

7. SCREENING VISIT 2 (SV2) 2

Setting 2

Preparations for SV2 2

Conducting SV2 3

Confirm ID, check visit window, and obtain informed consent 3
Review/complete Eligibility Questionnaire 3
Assess blood pressure 4
Measure participant's weight and height and check BMI 4
Collect urine sample for dipstick measures of protein and glucose 4
Complete the review of the Eligibility Questionnaire 5
Collect blood samples for local exclusionary labs 5
Distribute and instruct on The Food Frequency Questionnaire (Form #09) 5
Distribute instructions and urine container for the 24-Hour urine sample 5
SV2 Visit Form 5

Ending SV2 6

7. Screening Visit 2 (SV2)

Purpose

The purpose of SV2 is to continue to identify ineligible participants as accurately and efficiently as possible. The activities of SV2 are listed below and include a review of the Eligibility Questionnaire; measurement of blood pressure, height (if not measured at SV1), and weight (if not measured at SV1); collection of urine and blood samples; and distribution of the instructions and supplies for the Food Frequency Questionnaire and the 24-hour urine collection, both of which are to be completed by the participant before SV3.

Setting

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

Preparations for SV2

The following materials are needed to conduct the SV2.

- Random zero (RZ) sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- Stadiometer
- Scale
- Local laboratory chemistry panel blood supplies
- Urine dipsticks and urine sample containers
- Local Lab Worksheet (Form #14)
- Participant instructions and materials for 24-hour urine collection
- Consent materials (if required by local IRB, see Chapter 3)
- Food Frequency Questionnaire (Form #09)
- SV2 Visit Form (Form #05)
- SV2 Blood Pressure Form (Form #04)
- Study charts for scheduled participants

The following forms may also be needed and should therefore be on hand.

- Blank Eligibility Questionnaire (Form #06)
- Participant Closeout Form (Form #18)
- BMI Reference Chart (included at back of chapter)

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

Conducting SV2

In general, performing the SV2 activities in the order listed below should provide the most efficient identification of ineligible subjects. SV2 may be politely concluded at any point after an exclusionary condition or situation has been identified.

- Attach pre-printed participant labels for all forms
- Confirm participant ID, check visit window, and obtain informed consent
- Briefly review the Eligibility Questionnaire for obvious exclusions
- Take two RZ blood pressure readings and complete SV2 Blood Pressure Form
- Weigh participant, measure height, and check BMI (if not already done at SV1)
- Collect urine sample for dipstick measures of protein and glucose
- Collect blood samples for local exclusionary labs
- Distribute Food Frequency Questionnaire and instruct participant in its use
- Distribute instructions and urine container for the 24-hour urine sample - instruct women to make the 24-hour urine collection when they are not menstruating
- Record events and eligibility status on the SV2 Visit Form

Confirm ID, check visit window, and obtain informed consent

Check to make sure that at least seven days have transpired since the blood pressure was taken during the SV1 visit. No upper limit exists for the SV2 window, except that run-in cannot begin more than 150 days past SV1.

If necessary, obtain informed consent for the visit.

Review/complete Eligibility Questionnaire

The participant may have the Eligibility Questionnaire completed (except the medication and over the counter products review) at SV1. If so, then it does not need to be completed again. Check to see if it is in the participant's study chart and, if so, mark the "Done?" and eligibility status on the SV2 Visit Form.

If a completed Eligibility Questionnaire is not in the participant's study chart, he should be bringing one with him to the SV2 visit along with all of his medication bottles, vitamin bottles, and any other supplements he is taking. The "office use only" section of the questionnaire should be in the chart.

Before proceeding with the remainder of the visit, a staff person should briefly review the questionnaire for obvious exclusions and, if any are found, apologize and excuse the subject.

Clarification of items and a review of the medications can be deferred to later in the visit. Detailed instructions for reviewing the form and determining eligibility may be found in the DASH2 Forms Manual.

Once the questionnaire review is complete, check the "Done?" box on the SV2 Visit Form and record the appropriate eligibility status.

If the participant fails to bring the form with him to the visit, have him complete a new form. It will be necessary to call the participant at home to review his medications.

Assess blood pressure

Take the participant's blood pressure using the RZ device and the procedures described in MOP Chapter 11 (Blood Pressure Assessment). **Be sure to use the same cuff size as was used in SV1.** If the average of the SV1 and SV2 systolic blood pressure measurements is between 119 and 165 mm Hg and the average of the SV1 and SV2 diastolic blood pressure measurements is between 79 and 98 mm Hg (inclusive), the participant is eligible to continue to SV3.

If the cumulative average of the SV1 and SV2 SBP measurements is >180 mm Hg or the cumulative average of the SV1 and SV2 DBP measurements is >110 mm Hg, the participant is not only excluded from further participation but must be referred to a physician. The participant may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment even if the BP is lower than the above limits. The BP escape tracking form must be filled out and a copy filed in the participant chart at the site and a copy sent to the CC.

If the cuff size is found to differ from that used during SV1 and the participant has not left the clinic, a replacement blood pressure should be taken using the proper cuff. Otherwise, the original measurement will stand.

Measure participant's weight and height and check BMI

If not done at SV1, measure the participant's weight and height per the protocol outlined in MOP chapter 13. Note the BMI eligibility status on the SV2 Visit Form. Refer to the SV2 Reference Chart (located in the back of this chapter) to determine if the participant is BMI eligible.

Collect urine sample for dipstick measures of protein and glucose

Collect a urine sample from the participant, measure protein and glucose using the appropriate dipstick devices, and record on the SV2 Visit Form. The participant is ineligible if either the urine dipstick protein is greater than ≥ 2 or the urine dipstick glucose is positive, although each site has the option of conducting a confirmatory test at a later time.

If the results are not acceptable and the participant will not be retested, check the "ineligible" box under Visit Outcome on the SV2 Visit Form. If the results are acceptable or the participant will be retested, initiate the Local Lab Worksheet, enter the results and details of retesting (if appropriate). The participant is considered eligible for purposes of the SV2 Visit Form.

Complete the review of the Eligibility Questionnaire

Complete the review of the Eligibility Questionnaire, clarifying the participant's questions or comments. Record results on SV2 Flow Form. Confirm list of medications with medication bottles. If the participant is eligible to continue and medications were listed on the back page, a DASH2 clinician must review and sign the form assuring that the participant is not taking any medications or over-the-counter products that would make her ineligible.

Collect blood samples for local exclusionary labs

Draw the necessary blood samples for the local exclusionary labs. Follow the procedures outlined in MOP Chapter 12 for collection and processing. Remind participant that you may recall him for additional blood draws if any questions arise on these tests. The Local Lab Worksheet (Form # 14) is used to track whether the specimens are collected, if a repeat test is ordered, and the eligibility status of the participant based on the results of each test. The Local Lab Worksheet should be initiated at this point if it has not been done previously.

Distribute and instruct on the Food Frequency Questionnaire (Form #09)

Distribute the Food Frequency Questionnaire to the participant and review the instructions in the DASH2 Forms Manual for filling it out. Inform the participant that she needs to bring the completed form back with her to the SV3 visit. Make sure that the participant's label is on each page the form.

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

Distribute the 24-hour urine container and instructions to the participant and review the instructions with the participant. Inform the participant that she needs to bring the container back within 24 hours of collection, and that it must be returned at or before the SV3 visit. Make sure that a label is affixed to the collection jug and that it is filled out with the appropriate identifying information. Refer to Chapter 12 of the MOP for detailed instructions.

Instruct women to make the 24-hour urine collection when they are not menstruating.

SV2 Visit Form

After each portion of the visit is completed, a DASH2 staff person should check the appropriate "Done?" box on the SV2 Visit Form and (if applicable) indicate whether the participant is eligi-

ble or not eligible to continue based on that portion of the visit. At the end of the visit a staff person should review this form to make sure that the participant has completed all of the necessary components. This person should also make sure that a single outcome status is coded at the bottom of the form and should enter his ID in the "Reviewed by staff ID" field.

If a participant is excluded at the investigator's discretion (i.e., not as part of the regular screening activities for this visit), check "ineligible" on the SV2 Visit Form and in addition complete the Participant Closeout Form (Form #18) to record the reason for the exclusion. This includes participants who are excluded because of high levels of urinary glucose and/or protein.

Ending SV2

To complete the SV2 visit, do the following:

- Inform the participant of eligibility status. You may inform the participant of eligibility status and terminate the visit wherever it is clear that the individual is not eligible for DASH2. Explain the reasons for ineligibility to participant. Enter the visit outcome status on the SV2 Visit Form.
- If eligible, schedule an appointment for SV3 at least seven days from SV2.
- Enter the outcome status on the SV2 Visit Form.
- Prepare and ship lab samples according to MOP procedures (Chapter 12).
- When all data on the SV2 Visit Form have been collected, enter the SV2 Visit Form, the SV2 BP Form and the Eligibility Form into the data entry/management system.

BMI Reference Chart

Body Mass Index Exclusion Cutpoints

Locate participant's height on the table below and note the accompanying maximum weight. If participant's weight equals or exceeds this value, the participant is ineligible based on BMI.

Height (cm)	Maximum weight (Kg)	Height (cm)	Maximum weight (Kg)
139	77.2	176	123.9
140	78.4	177	125.3
141	79.5	178	126.7
142	80.6	179	128.2
143	81.7	180	129.6
144	82.9	181	131.0
145	84.1	182	132.5
146	85.2	183	134.0
147	86.4	184	135.4
148	87.6	185	136.9
149	88.8	186	138.4
150	90.0	187	139.9
151	91.2	188	141.4
152	92.4	189	142.9
153	93.6	190	144.4
154	94.8	191	145.9
155	96.1	192	147.5
156	97.3	193	149.0
157	98.5	194	150.5
158	99.8	195	152.1
159	101.1	196	153.7
160	102.4	197	155.2
161	103.6	198	156.8
162	104.9	199	158.4
163	106.2	200	160.0
164	107.5	201	161.6
165	108.9	202	163.2
166	110.2	203	164.8
167	111.5	204	166.5
168	112.8	205	168.1
169	114.2	206	169.7
170	115.6	207	171.4
171	116.9	208	173.1
172	118.3	209	174.4
173	119.7	210	176.4
174	121.1	211	178.1
175	122.5	212	179.8
		213	181.5
		214	183.2

BMI=weight/ht^2 (Kg/m^2)---exclude if $\geq$40

8. SCREENING VISIT 3 (SV3) 3

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Summary of Edits

New changes in Version 1.1

- clarification regarding the collection of a fasting blood sample to be analyzed centrally

New changes in Version 1.2

- Collection of buffy coat sample added
- Removal of detailed instuctions regarding 24 hour urine collection that are found in MOP Chapter 12

8. Screening Visit 3 (SV3)

Purpose

The purpose of SV3 is to continue screening prospective participants for eligibility based on blood pressure and to collect data on physical activity and weight. The visit is also used to review the food frequency questionnaire, collect and process a 24-hour urine specimen, collect a fasting blood sample to be analyzed centrally, collect additional blood samples as needed for eligibility, and review in detail the study foods and menus with the participant.

Setting

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

Preparing for SV3

The following materials are needed to conduct the SV3.

- Random zero (RZ) sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- Scale
- Consent materials (if required by local IRB, see Chapter 3)
- SV3 Visit Form (Form #08)
- Study Foods Checklist (Form #101)
- SV3 Blood Pressure Form (Form #07)
- BP Escape Tracking Record (Form #23)
- Central Lab Collection Form - 24-hour urine (Form # 30)
- 24-hour urine collection materials
- DASH2 Study Menus (Form #102)
- Study charts for scheduled participants
- Physical Activity Questionnaire (Form #10)
- Symptoms Form (#11)
- Serious Adverse Events (Form #12)
- Local laboratory chemistry panel blood supplies
- Urine dipsticks and urine sample containers
- Local Lab Worksheet (Form #14)
- Central Lab Collection Form - Fasting Blood (Form #31)
- Participant instructions and materials for 24-hour urine collection
- Food Frequency Questionnaire (Form #09)

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

Conducting SV3

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

- Confirm participant ID, check visit window, and obtain informed consent
- Process 24-hour urine sample
- Take participant's RZ blood pressure readings and note eligibility on SV3 Visit Form
- Weigh participant and record on SV3 Visit Form
- Review Study Food Checklist (Form #101) with participant to identify possible problems and record eligibility on SV3 Visit Form
- Review DASH2 Study Menus (Form #102) with participant to identify possible problems
- Review participant's Food Frequency Questionnaire
- Review Local Lab Worksheet and collect additional laboratory specimens if needed
- Collect fasting blood sample to be analyzed centrally
- Collect buffy coat sample to be shipped to storage
- Administer Physical Activity Questionnaire (Form #10)
- Administer Symptoms Questionnaire (Form #11)

Confirm ID, Check Visit Window, and Obtain Informed Consent

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

If necessary, obtain informed consent for the visit.

Process 24-hour Urine Sample

The participant may have completed the 24-hour urine collection at any time between SV2 and SV3. Since the specimen should be returned within 24 hours of collection, the participant may or may not be bringing a specimen container with her to the SV3 visit. If she does not bring a container, check her study chart to confirm that she returned it previously and that it was an acceptable specimen.

Complete details on the processing of 24-hour urine specimens are contained in Clinic MOP Chapter 12 (Central Lab). The instructions for processing the specimen should be followed no

matter when the specimen is returned. The Central Lab Collection Form – 24-hour urine (Form #30) is used for processing the sample.

If the specimen is inadequate, or if the participant failed to bring it in, another (acceptable) specimen must be obtained prior to the start of run-in. Give the participant a new set of collection materials, attach and fill out the labels correctly, and write in "missing" next to "24-hour urine collection" on the SV3 Visit Form. If the participant is otherwise eligible to continue at the end of the visit, code "eligible" under Visit Outcome on the SV3 Visit Form.

Assess Blood Pressure

Take the participant's blood pressure using the RZ device and the procedures described in Clinic MOP Chapter 11 (Blood Pressure Assessment). **Be sure to use the same cuff size as was used at SV1.** Record the measurements on the SV3 Blood Pressure Form. If the sum of the SV1, SV2, and SV3 systolic blood pressure measurements is between 720 and 954 and the sum of the SV1, SV2, and SV3 diastolic blood pressure measurements is between 480 and 570 mm Hg (inclusive), the participant is (blood pressure) eligible to continue to run-in.

If the sum of the SV1, SV2 and SV3 SBP measurements is >1080 mm Hg or the sum of the SV1, SV2, and SV3 DBP measurements is >660 mm Hg, the participant is not only excluded from further participation, but must be referred to a physician for follow-up. The participant may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment even if the BP is lower than the above limits. The BP Escape Tracking Record (Form #23) must be completed and filed in the participant chart at the site and a copy sent to the CC.

If the participant cuff size is found to differ from that used during SV1 and the participant has not left the clinic, a replacement blood pressure should be taken using the proper cuff. Otherwise the original measurement stands.

Weigh Participant

Record the participant's weight per the protocol outlined in Clinic MOP Chapter 13. Enter this information on the SV3 Visit Form. This weight is not used for eligibility but instead is used to help determine the participant's target weight for feeding.

Review Study Food Checklist and DASH2 Study Menus with Participant

The SV1 visit included a brief review of common food items in the DASH2 diets to make sure the participant could eat them. During the SV3 visit a member of the clinic's nutrition staff should carefully review with the participant the Study Foods Checklist (Form #101) and the DASH2 Study Menus (Form #102). (See the DASH2 Diet MOP for details on this process.) The purpose of this review is to make sure that the participant is fully aware of the foods/menus that he may be fed and is willing to eat these foods. It is important that the participant be willing to comply with all dietary patterns. We do not want to randomize participants in the hope that

they will, for example, be assigned to the dietary patterns that they are willing to tolerate. It is much better, from the study's perspective, to exclude participants prior to randomization than to have them drop out of the study or be very noncompliant post-randomization. This is particularly true for cross-over trials.

This review, along with a review of the Food Frequency Questionnaire (see below), should take approximately 20 minutes. At the end of the review, the DASH2 staff person reviewing the foods should classify the participant as eligible or ineligible to continue based on the review. This should then be noted on the SV3 Visit Form.

Review Participant's Food Frequency Questionnaire

The participant should have brought in the completed Food Frequency Questionnaire (FFQ). If so, review it for completeness, resolve any unanswered questions or invalid responses, and check the appropriate "Done?" box on the SV3 Visit Form. The FFQ will be sent to the coordinating center for batch entry and will become part of the central database. The FFQ Shipping Log (Form #36) is used to process the FFQs.

If the participant did not return a completed FFQ, give her a new one, reinstruct her on its use, and ask her to complete it. If she is unable to complete it at the visit, ask her to mail it in and arrange a time for review. A completed FFQ should be returned and reviewed for completeness (or "refused" indicated).

Collect Additional Laboratory Specimens if Needed for Eligibility

For participants whose SV2 exclusionary labs came back as ineligible, clinics have the option of repeating the analyses once. (For renal insufficiency, cholesterol, and glucose/insulin, the protocol for repeat analyses is somewhat more complex. Refer to Clinic MOP Chapter 4 for details).

If the participant needs additional blood drawn, this can be done at this point. Note that some of the repeat tests require a fasting sample. In this case, the participant should have been instructed ahead of time to fast prior to the visit, and this should be confirmed at the time of the visit. If a repeat blood is drawn, record that on the Local Lab Worksheet (Form # 14). Check the appropriate "Done?" box on the SV3 Visit Form to indicate that the laboratory review was conducted.

Similarly the urine dipstick protein may be repeated at this visit. The participant is ineligible if the urine dipstick protein is $\geq$2+. Record the result and check the appropriate box to indicate if he is ineligible on the SV2 Visit Form.

Collect Fasting Blood Sample to be Analyzed Centrally

A fasting blood sample must be collected at SV3 or prior to the beginning of run-in. Record the information on the Central Lab Collection Form - Fasting Blood (Form #31). The participant must have fasted for a period of 8-14 hours prior to drawing the sample. It is to be sent to the central lab (see Clinic MOP chapter 12) for processing.

Collect Buffy Coat Sample

The buffy coat sample must be collected at SV3. Record the information on the Central Lab Collection Form – Fasting Blood (Form #31). It is to be sent to storage (see Clinic MOP Chapter 12) for processing information.

Administer Physical Activity Questionnaire

Complete the Physical Activity Questionnaire (Form #10). The computer will compute an initial caloric level to be used to start the run-in feeding. This value will be printed out as part of the participant randomization report after the data has been entered. Check the appropriate "Done?" box on the SV3 Visit Form.

Administer Symptoms Form

Complete the Symptoms Form (#11) with the participant. Check the appropriate "Done?" box on the SV3 Visit Form. If participant answers yes to question 17, the staff person must fill out the Serious Adverse Events Form (Form #12). The Serious Adverse Events Forms are photocopied and the original sent to the Coordinating Center to be filed in the participant charts. In the event of a serious adverse event, the study clinician takes any appropriate action to insure the safety of the participant (e.g., referral for evaluation or treatment).

Ending SV3

To complete the SV3 visit, do the following:

- Review SV3 Visit Form to make sure visit is complete.
- Inform the participant of eligibility status. You may inform the participant of eligibility status and terminate the visit at any point that it is clear that the individual is not eligible for DASH2. Explain the reasons for ineligibility to the participant. Enter the visit outcome status on the SV3 Visit Form. Enter the SV3 Visit Form, the Physical Activity Questionnaire, and the Symptoms Form into the data entry/management application. These forms needs to be entered within one week of the SV3 visit.
- If the participant is eligible for run-in, remind her of the start date and provide other instructions as appropriate so that she is ready to begin. Remind participant, if needed, that final eligibility for run-in will depend on results of pending laboratory tests and the completion of pending questionnaires. In addition, remind the participant of the requirement to maintain her current weight between this visit and the start of run-in for continued eligibility. Give information on the individual weight limits for eligibility and tips on maintaining weight.
- If the participant was excluded due to escape-level blood pressure criteria, refer him to his physician and complete the BP Escape Tracking Record.
- Send Food Frequency Questionnaire to the Coordinating Center
- Prepare and ship lab samples to be analyzed centrally according to Clinic MOP (Chapter 12) procedures.

9. RUN-IN AND RANDOMIZATION 3

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Summary of Edits

New changes in version 1.1

- Clarification of randomization process
- Measurement of arm circumference on RI-1
- Collection of Diet Acceptability Questionnaire

New changes in version 1.2

- Clarifies who is to administer the Diet Acceptability Questionnaire
- Changed references to Serious Adverse Event forms to Adverse Event forms
- Modified the procedure for handling Adverse Event forms

9. Run-In and Randomization

Overview

All participants who are eligible based on the three screening visits undergo a run-in period on the control diet (alternatively described as the "A" diet in the Diet MOP) prior to randomization. The run-in phase has two main objectives: 1) to identify and exclude individuals who will not comply with the trial's eating and measurement requirements, and 2) to determine, for each participant, the appropriate energy level needed to maintain weight. The World Health Organization's equations, which are based on age, gender, and weight, are used to estimate resting energy expenditure. Total energy requirement is estimated by multiplying the resting energy expenditure by a factor indicating overall physical activity level based on the Stanford 7-Day Physical Activity Questionnaire. (see DASH2 Diet MOP, Chapter 36).

Run-in feeding must begin within 150 days of SV1, and all laboratory eligibility criteria must be met prior to the start of run-in. In addition, if the Eligibility Questionnaire (Form #6) is completed more than one month before run-in begins, the Eligibility Review (Form #13) must be completed within one month of the start of run-in. During the run-in period, participants receive all of their food from the clinic and are required to attend the clinic for at least one meal per day, five days per week, preferably lunch or dinner. For logistical reasons, the clinics conduct the feeding in four successive cohorts over a period of two years. In order to allow for dropouts and exclusions during the run-in phase, the run-in cohorts should include between 28-30 participants per site.

Run-in feedings are scheduled to start on the same day for all participants in a given feeding cohort in a given clinic. However, participants may be allowed to start run-in feeding up to two days late if the clinic determines that the delay is due to exceptional circumstances not likely to affect future compliance. In this latter case, the length of run-in feeding for those participants is shortened so that all subjects are scheduled to finish run-in feeding on the same day.

The duration of run-in feeding may vary between 12 and 14 days, is determined locally, and may vary from cohort to cohort. **To provide consistent terminology, we shall refer to these as run-in days 0 through 14, and shall use the notation RI-0...RI-14.** Thus a participant who starts run-in feeding two days late is said to start on run-in day 2 (RI-2).

Because feeding does not begin with the breakfast meal, the first and last days of run-in feeding represent partial feeding days. For example, if feeding begins with dinner, then only dinner is fed on run-in day 0 and only breakfast and lunch are fed on run-in day 14. All data gathered on run-in day 14 will be assigned to that day, even if this coincides with the initial day of intervention feeding. In order for study measurements to reflect the effect of the diets, no study measurements are taken on run-in day 0 or, if a participant starts late, on the initial day of feeding.

In order for the clinics to assemble and prepare the necessary foods for the start of intervention feeding, randomization occurs midway through the second week of run-in feeding rather than at the end of the run-in period. Neither the participants nor the staff conducting measurements are told the randomization assignment. Only staff involved in meal preparation are allowed to be unblinded to treatment allocation. There is an optional break of up to three days (nine meals) between the end of run-in and the beginning of the initial intervention feeding period. Subsequent intervention feeding periods may be separated by breaks of up to five days(15 meals) in duration. These breaks are not mandatory, and their duration may vary, from site-to-site within a cohort, and from cohort-to-cohort. During the breaks between feeding periods, subjects are not provided any food and are allowed to return to their original diets.

Preparing for Run-In

Prior to the start of run-in, all eligibility information needs to be completed. This includes the results of any eligibility laboratory work completed between SV3 and run-in. If the Eligibility Questionnaire (Form #06) was completed more than one month prior to the start of run-in, the Eligibility Review (Form #13) must be completed within one month of the start of run-in. In addition, a fasting blood sample to be analyzed centrally must be collected prior to the start of run-in.

Run-in consists of a series of visits, the preparations for which may vary from day-to-day. Certain aspects, such as those related to the preparation and distribution of food, are nearly identical from day to day. Other activities, such as blood draws and blood pressure assessment, happen much less frequently. Table 9.1 lists the various activities that take place during run-in. Food preparation, feeding, and compliance assessment are comprehensively discussed in the DASH2 Diet MOP.

Materials Needed During Run-In

- Consent form (if needed)
- Run-in Flow Form (# 16)
- Scale
- Daily Diary (Form # 24)
- Patient History Questionnaire (Form #19)
- Random zero (RZ) sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- Initial Run-In Blood Pressure Form (#37)
- Generic Blood Pressure Form (#15)
- BP Escape Tracking Record (Form #23)
- Anthropometric measuring tape
- Symptoms Form (# 11)
- Adverse Events Form (#12)
- Medication Questionnaire (# 17)

- Case Conference Form (# 33)
- Study charts for scheduled participants
- Participant Closeout Form (#18)
- Premature Study Termination Form (#22)
- Diet Acceptability Questionnaire (Form # 35)

Table 9.1
DASH2 Activity Sequence: Run-in Feeding Period

	------- Day of Run-in --------														
Run-in Event	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13***	**14**
RZ Blood Pressure (2 sets only)	<====== One set per week =====>								<==== One set per week ====>						
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Run-in Feeding Activities	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient History Questionnaire	<========== Any time during Run-In ==========>														
Measure Waist Circumference	<========== Any time during Run-In ==========>														
Medication Questionnaire									<========== X ==========>						
Diet Acceptability Form									<========== X ==========>						
Symptoms Form									<========== X ==========>						
Case Conference									<==== X ===>						
Resolution of Data Issues									<==== X ===>						
Randomization												X			
Compliance Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	

* optional, may vary from site-to-site and from cohort-to-cohort within a site.

Run-In Activities

Obtain Informed Consent If Needed

If necessary, obtain informed consent for the run-in phase prior to the start of run-in feeding. Presumably this will have been done prior to run-in day 0, but if not, then it must be done at this time. Check the appropriate box on the Run-In Flow Form (#16) when it is completed.

Measure Weight at Each Clinic Visit

All participants are weighed at each clinic visit during the run-in and intervention phases of the trial. Use the procedures outlined in Clinic MOP chapter 13. **All participants whose weight**

changes by five percent or more between SV3 and the first full day of run-in (RI-1) are excluded from the trial at that point After taking the RI-1 weight, record the eligibility status on the Run-In Flow Form (#16).

The average of the SV3 weight measurement and the first two run-in weights (those taken on RI-1 and RI-2) defines the participant's **target weight** and is used as the baseline against which to measure weight change during run-in feeding. As noted in Diet MOP chapter 41 (Participant Management and Compliance), weight is not supposed to change during the study. These daily weight measurements are used to monitor weight changes, and the overall caloric content of the participant's meals is adjusted as needed in order to assure that the participant's weight remains stable throughout the study. The weight is recorded on the Daily Diary (Form #24). The weight data should be entered daily so that the weight tracking reports generated from the data entry/management application can be reviewed daily.

Collect Remaining Baseline Blood Pressure Measurements

As part of each participant's baseline blood pressure measurements, the Protocol requires that one set of blood pressure measurements be taken during each week of run-in feeding. Clinic staff should measure blood pressure using an RZ device and follow the procedures described in Clinic MOP chapter 11 (Blood Pressure Assessment). Because of the potential time lapse between SV3 and run-in, there may be changes in weight or body composition that would change the arm circumference and the appropriate cuff size used to measure BP. In order to determine accurate cuff size, measure the arm circumference again at the time of the first run-in blood pressure assessment and record it on the Initial Run-In Blood Pressure Form (#37). The appropriate cuff size is also recorded on the Initial Run-In Blood Pressure Form (#37).

Of necessity, some of the run-in blood pressure measurements will occur after randomization. In order to minimize the potential for subjective biases in the measurement, the clinic staff who measure blood pressures during run-in must be blinded to intervention assignment.

Other than for escape level exclusions, the run-in blood pressure measurements are not used to determine eligibility; they are used only to help calculate baseline blood pressure. The Protocol defines two blood pressure escape levels during run-in.. Escape level 1 is defined as a single day's average SBP measurement in excess of 180 mmHg or a single day's average DBP in excess of 110 mmHg. Escape level 2 is defined as a single day's average SBP measurement in excess of 170 mmHg or a single day's average DBP measurement in excess of 105 mmHg. In each case, the appropriate follow-up actions are discussed in Clinic MOP Chapter 18, Safety Monitoring. If a participant hits an escape level, complete the BP Escape Tracking Record (Form #23).

Persistently elevated blood pressure during run-in results in exclusion from further participation in the trial and referral to a physician, regardless of whether the participant has already been randomized. **Participants reaching blood pressure escape limits may not begin intervention**

feeding unless a subsequent blood pressure measurement, taken within the appropriate time frame, falls within acceptable limits (as defined in Chapter 18, Safety Monitoring.)

The blood pressure measurement taken during the second week of run-in is recorded on the Generic Blood Pressure Form (#15) and is entered into the data system at the clinical center. The entry of the two blood pressure readings taken during run-in are not required before randomization occurs. They do, however, need to be entered within seven days after the end of run-in. Check the appropriate boxes on the Run-In Flow Form (#16) as they are collected.

Complete Patient History Questionnaire

Sometime during run-in, and preferably before randomization, the participants complete the Patient History Questionnaire (Form #19). This is a self-administered questionnaire that can be completed at home. Clinic staff should review returned questionnaires for completeness and should resolve any unanswered or vague responses. The forms are entered on-site within 7 days. Check the appropriate box on the Run-In Flow Form (#16) when the form is collected.

Measure Waist Circumference

Each participant's waist circumference is measured during run-in but not on RI-0. Participant's should be advised in advance that partial disrobing at the waist will be required at this visit. This measurement must be made by certified staff using the protocol outlined in Clinic MOP Chapter 13. Measurements are recorded on Run-In Flow Form (form #16) and are entered on-site within 7 days.

Complete Symptoms Form

All participants complete the Symptoms Form (Form #11) in the last week of run-in. It is best to complete it as late as possible in run-in while still feeding. The questionnaire, which is repeated towards the end of each intervention feeding period, is primarily designed to document gastrointestinal symptoms associated with the diets. Completed questionnaires are entered on-site within 7 days. Check the appropriate box on the Run-In Flow Form (#16) when it is collected.

The Symptoms Form should be completed by participants and reviewed by clinic staff for completeness. Any positive responses must be reviewed by a study clinician, who determines if further follow-up is needed. Positive responses to the final question (q17), relating to the occurrence of serious adverse events, trigger the completion of an Adverse Events Form (#12).

After entry into the DASH2 data entry system, the Adverse Events Forms are photocopied and the original sent to the Coordinating Center to be filed in the participant charts. The photocopy should be filed in the participant chart at the site. In the event of a serious adverse event, the study clinician takes any appropriate action to insure the safety of the participant (e.g., referral for evaluation or treatment).

Complete Medication Questionnaire

All participants complete the Medication Questionnaire (Form #17) during the last week of run-in. It is best to complete it as late as possible in run-in while still feeding. The questionnaire, which is repeated towards the end of each intervention feeding period, is designed to identify those individuals who start taking medications during the course of the study.

The questionnaire should be administered in an interview format, and all positive responses must be reviewed by a staff clinician. Individuals taking exclusionary medications (see Clinic MOP Chapter 4) must either stop taking these medications or be excluded from further participation in the study. Completed questionnaires will be entered on-site within 7 days. Check the appropriate box on the Run-In Flow Form (#16) when the form is collected.

Complete Diet Acceptability Questionnaire

All participants complete the Diet Acceptability Questionnaire (Form # 35) during the last week of run-in. It is best to complete it as late as possible in run-in while still feeding. Dietary staff should administer the questionnaire and review returned questionnaires for completeness. The forms are to be entered on-site within 7 days.

Prepare And Distribute Daily Meals

Kitchen staff must prepare and distribute food for participants on an ongoing basis throughout run-in. Details of food preparation are given in the Diet MOP Chapter 40.

Review Daily Food Diaries to Assess Compliance

Kitchen staff must assess compliance with the study's eating requirements on an ongoing basis. Details on compliance monitoring are given in the Diet MOP Chapter 41.

Conduct Overall Compliance Assessment/Case Conference

In addition to the exclusionary criteria applied during the screening visits, participants may be excluded during run-in for unusually large weight swings or for noncompliance with the protocol**.** Participants may also be excluded prior to randomization for missed meals, poor clinic attendance, and over- or-under consumption of food. Finally, clinics subjectively evaluate each participant's overall compliance and attitude just prior to randomization and may exclude participants on the basis of this assessment as well. This is referred to as a case conference and the Case Conference Form (#33) is completed. Completed forms will be entered on-site and must be done so prior to randomization. Check the appropriate box on the Run-In Flow Form (#16) when the case conference is completed. A more detailed discussion of compliance assessment is provided in the Diet MOP Chapter 41. If the participant is excluded by the case conference, the Participant Closeout Form (#18) must be completed.

Randomize Participant

Randomization occurs during the second week and prior to the end of run-in feeding. The timing of randomization may vary from cohort to cohort, provided that it occurs at least nine days after the start of run-in feeding and at least three working days prior to the start of intervention feeding. The former criterion permits adequate assessment of dietary compliance, while the latter assures that the kitchen staff have adequate time to assemble and prepare the foods that are needed for the start of intervention feeding (they need to know each participant's dietary assignment). Within a given feeding cohort at any given site, however, all participants are randomized at the same time.

Following randomization, participants remain on the run-in diet until the run-in period ends. Participants are not told to which group they have been assigned and, except for staff involved in meal preparation, clinic personnel are also blinded to intervention assignment. Blinding is discussed further in Clinic MOP Chapter 14 (Quality Control and Data Management).

Randomization is stratified by clinic and, within each clinic, structured to assure comparable treatment group sizes over time with respect to both dietary pattern assignment and the sequence in which the sodium levels are administered. Although randomization is not stratified by gender, race, or baseline hypertensive status, the distribution of these factors across the treatment groups is monitored to assure that a balanced distribution is achieved.

The timing of events to complete randomization within the three-day window demands tight coordination between the Coordinating Center and the intervention sites. The following timeline is recommended to ensure adequate time to resolve all pre-randomization issues and to give kitchen staff adequate time to prepare for intervention. However, as long as all the appropriate data are entered and the data issues resolved, the randomization can be done as early as RI-9. If the site has a break between run-in and intervention, the randomization date can also be pushed back if need be. There needs to be a three-working-day preparation time between randomization and the start of intervention feeding, however.

The actual process of randomization is discussed in detail in the DASH2 Data Management Manual.

Day 9: <u>All</u> data at least through RI-8 need to be entered in the file server by the end of RI-9. These data include the Daily Diary (Form #24) from days 1-8, the Case Conference Form (#33), and all screening data not previously entered.

Day 10: The clinic coordinator at each site prints a randomization eligibility report from the data management system for each run-in participant. If a participant appears to be ineligible for randomization, the reason(s) will be listed on this report. The clinic coordinators need to <u>immediately</u> review these reports to confirm that the information matches their records. If corrections are needed, the clinic coordinator will need to call Reesa Laws at the CC make necessary corrections.

Day 11: Randomization can be done only after the data are complete and corrected. The clinic coordinator will indicate in the data management system each person that is to be randomized and notify the dietitian or the unblinded designee that the randomization is done and the Treatment Assignment Report may be printed. This password-protected report should be printed out and shared only with kitchen staff who need to be unblinded to treatment status.

End Run-In

Remind subjects of dates and procedures for starting Intervention Feeding Period 1, and dismiss them for the break period (if applicable).

10. INTERVENTION 3

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Summary of Edits

New Changes in Version 1.1

- Change collection days for the Diet Acceptability Questionnaire
- Moved detailed instructions of collection of 24-hour urine to Chapter 12
- Remove reference to buffy coat samples (done in SV3)
- Change instructions for collection of samples for renin analysis

New Changes in Version 1.2

- Change instructions for the Diet Acceptability Questionnaire
- Change definition of baseline weight
- Change instructions for Participation Survey
- Clarify information on Exit Interview
- Changed references to Serious Adverse Event form to Adverse Event form
- Modified the procedure for handling Adverse Event forms

New Changes in Version 1.3

- Change in window for final two RZ measurements each feeding period

10. Intervention

Overview

The three-month intervention feeding period begins 0 - 3 days (up to 9 meals) after the end of run-in (12-17 days after the start of run-in feeding). During this period participants continue to receive all of their food from the clinic and to eat on-site at least one meal per day, five days per week. As with the run-in feeding, the on-site meal should be a lunch or dinner if possible. Intervention feeding is divided into three separate one-month (30-day) feeding periods, each at a different level of sodium intake. Feeding periods 1&2 and 2&3 may be separated by breaks of up to five days (15 meals), during which subjects return to their usual diets.

To provide consistent terminology, we shall refer to the three months of intervention feeding as ***intervention feeding periods I, II, and III***. Within each intervention feeding period, days are numbered 0-30. Thus, intervention feeding period I, day 10 can be written as IFP/I-10, and intervention feeding period III, day 30 can be written as IFP/III-30.

Because feeding does not begin with the breakfast meal, the first and last days of each feeding period represent partial feeding days. For example, if feeding begins with dinner, then only dinner is fed on day 0 and only breakfast and lunch are fed on day 30. Thus the feeding periods cover 31 calendar days but only 30 metabolic days. In order for study measurements to reflect the effect of the diets, no study measurements are taken on feeding day zeros.

Weight is recorded at each clinic visit and blood pressure is assessed weekly during the first three weeks of each intervention feeding period. A blood pressure assessment consists of a single day's set of two measurements. During the **final 9 days** of each intervention feeding period, the following procedures are performed:

1. Five sets of daily blood pressure measurements are recorded, including at least two sets during the final three days.
2. A 24-hour ABPM reading is recorded.
3. A 24-hour urine is collected.
4. A Fasting blood sample is collected.

A sample from the 24-hour urine specimen is sent to a central laboratory for assessment of Na, K, Ca, urea nitrogen, phosphorus, and creatinine for group analyses. Samples of urine, serum, and plasma are also frozen and stored for future analyses.

During the **final 7 days** of each intervention period the following procedures are also performed:

1. Formal side effects assessment
2. Medication use monitoring
3. A brief assessment of physical activity
4. Completion of an anonymous survey
5. Assessment of diet acceptability (also measured between days 7 and 9)

At the conclusion of each feeding cohort (i.e., at the end of IFP/III), study participants receive a summary of their study blood pressures and dietary counseling for heart disease prevention. They also complete a participation survey (Form # 26) at this time.

Preparing for Intervention

Intervention consists of a series of visits, the preparations for which vary from day-to-day. Certain aspects, such as those related to the preparation and distribution of food, are nearly identical from day-to-day. Other activities, such as blood draws and blood pressure assessment, happen much less frequently. Table 10.1 lists the various activities that take place during the intervention feeding phase. Comprehensive discussions of food preparation, feeding, and compliance assessment are provided in the DASH2 Diet MOP.

Materials Needed During Intervention.

- Random zero (RZ) sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- Generic Blood Pressure Form (#15)
- BP Escape Tracking Record (Form #23)
- ABPM devices
- ABPM Placement Form (#27)
- ABPM Participant Form (#28)
- ABPM Instructions to Participants (Form #60)
- ABPM Initialization/Downloading Checklist (Form #59)
- Central laboratory supplies (see Chapter 12)
- Central Lab Collection Form - Fasting Blood (Form #31)
- Participant instructions and materials for 24-hour urine collection (see Chapter 12)
- Central Lab Collection Form - 24-hour urine (Form #30)
- Scale
- Daily Diary (Form #24)
- Intervention Flow Form (#20)
- Brief Physical Activity Questionnaire (Form #21)
- Symptoms Form (#11)
- Adverse Events Form (#12)
- Medication Questionnaire (Form #17)
- Anonymous Survey (Form #25)
- Diet Acceptability Survey (Form #35)
- Participation Survey (Form #26)
- Study charts for scheduled participants
- Premature Study Termination Form (#22)

Table 10-1
DASH2 Activity Sequence

Intervention Feeding Period

Event	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
RZ BP ^		<===	===X===	===>		<===	===X===	====>		<===	===X===	====>		<===	===X===	====>		<===	===X===	====>		<===	===X===	===>	<=	X=	=>				
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-HR urine																							<===	=====	===X	=====	===>				
ABPM																							<===	=====	===X	=====	===>				
Fasting Blood Draw																							<===	=====	===X	=====	===>				
Medication Questionnaire																									<===	=====	===X	=====	===>		
Symptoms Questionnaire																									<===	=====	===X	=====	===>		
Anonymous Survey																									<===	=====	===X	=====	===>		
Brief Physical Activity																									<===	=====	===X	=====	===>		
Diet Acceptability Questionnaire								<===	X==	===>																			<==	==X	==>
Intervention Feeding	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	X																														
Compliance Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
		X																													
Participation Survey*																											<===	=====	===X	=====	===>
Exit Interview and Counseling*																															X

^ once per week during days 1-21; five times during the final 9 days, including at least twice during days 28-30 of each feeding period.

* done at the end of the third intervention period (IFP-III) only

Blood pressure and weight measurements are always taken prior to eating, with the exception that no measurements are made on intervention feeding days zero. Collection of the fasting blood samples must also be done prior to eating and after an 8-14 hour fast. The timing of other one-time activities (i.e., before or after eating) is left to clinic discretion.

In the event that no gaps are used between feeding periods, the beginning of one feeding period can coincide with the end of the previous period. For example, RI-14 could coincide with IFP/I-0, or IFP/II-30 could coincide with IFP/III-0. In these cases blood pressure and weight measurements taken on these days would be assigned to the feeding period that is concluding.

Intervention Activities Occurring During Each Iintervention Feeding Period

Measure Weight at Each Clinic Visit

All participants are weighed at each clinic visit (except days zero) during the intervention phase of the trial using the protocol outlined in Clinic MOP Chapter 13. The average of all weight measurements recorded during run-in feeding plus the weight taken at SV3 defines the participant's **baseline weight** and is used as the baseline against which to measure weight change during intervention feeding. The daily weight measurements recorded during intervention are used to monitor for weight changes, and the overall caloric content of each participant's meals is adjusted as needed to assure that weight remains stable throughout the study. The daily weight is recorded on the Daily Diary (Form #24).

Collect Blood Pressure Measurements

As part of each participant's final blood pressure measurements, the Protocol requires that five sets of blood pressure measurements be taken during the final 9 days of each intervention feeding period, and that at least two of these five should be taken during the last three days of intervention feeding (i.e., days 28, 29, and 30). In addition, blood pressure is assessed once (set of two RZ measurements) during each of weeks one through three (days 1-21) of each intervention feeding period. These latter blood pressures, under no circumstances, should be taken on the first day of an intervention feeding period (i.e., day 0).

Clinic staff measure blood pressure using an RZ device and follow the procedures described in Clinic MOP Chapter 11 (Blood Pressure Assessment). In order to minimize the potential for subjective biases, **the clinic staff who measure blood pressure must be blinded to each participant's intervention assignment. Also, please be sure that all blood pressure measurements are made using the same cuff size as was used at the beginning of run-in**. If the cuff size is found to differ from that used during run-in and the participant has not left the clinic, a replacement blood pressure should be taken using the proper cuff. Otherwise the original measurement stands.

In order to ensure participant safety, blood pressure thresholds are established that trigger repeat measurements and medical referral. These limits are discussed in chapter 18, Safety Monitoring.

Participants who are started on blood pressure medication are excluded from further participation in the trial. Clinic staff should therefore attempt to obtain as many daily blood pressure measurements as possible (up to a maximum of five days) from the time a participant is referred to her provider until such time as she starts on medication. If the participant's provider decides that she does not need to go on medications, then the participant should continue to be followed in the study as usual. However, the clinic staff should still have attempted to collect the five blood pressure measurements as a precaution. Complete the BP Escape Tracking Record (Form # 23).

For reasons of safety, participants should not be asked to defer the start of therapy in order that the clinic be able to obtain a complete set of five measurements.

The intervention blood pressure measurements are recorded visit on the Generic Blood Pressure Form (#15). Data should be entered within seven days of collection.

Collect a 24-Hour Urine Sample at End of Each Feeding Period

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

A 24-hour urine specimen needs to be collected during days 22-30 of each intervention feeding period. A sample from this specimen is sent to the central laboratory for processing for subsequent group analyses. Details on the processing of 24-hour urine specimens are contained in Clinic MOP Chapter 12. The Central Lab Collection Form - 24-hour urine (Form #30) is used for tracking the 24-hour urine sample. Check the appropriate box on the Intervention Flow Form (#20) when the sample has been collected and the form is completed.

Collect ABPM Data

All participants complete a period of 24-hour ambulatory blood pressure monitoring sometime during days 22-30 of each intervention feeding period. Instructions for performing the measurement and downloading the data are given in Clinic MOP Chapter 20. The Coordinating Center retrieves the blood pressure data from the file server. Completed ABPM questionnaires are entered on-site within seven days of collection. Check the appropriate box on the Intervention Flow Form (#20) when this is completed.

Collect Fasting Blood Sample

During days 22-30 of intervention feeding subjects must provide a fasting blood sample. To be valid, the participant must have been fasting for a period of 8-14 hours and must have been in an upright position (defined as seated or standing) for at least 1½ hours prior to the blood draw. The requirement to have been in an upright position for 1½ hours is a target. Details on drawing and processing this specimen are given in Clinic MOP Chapter 12(Central Lab). The Central Lab Collection Form-Fasting Blood (#31) is used for tracking the specimen. Check the

appropriate box on the Intervention Flow Form (#20) when the sample is collected and the form is completed.

Complete Symptoms Form

All participants complete the Symptoms Form (#11) between days 24-30 of each intervention feeding period. The questionnaire is primarily designed to document gastrointestinal symptoms associated with the diets. Completed questionnaires are entered on-site within 7 days. Check the appropriate box on the Intervention Flow Form (#20) when this is completed.

The questionnaire should be completed by the participant and reviewed by clinic staff for completeness. Any positive responses must be reviewed by a study clinician, who determines if further follow-up is needed. Positive responses to the final question (q17), relating to the occurrence of serious adverse events, trigger the completion of an Adverse Events Form (#12). After entry into the DASH2 data entry system, the completed Adverse Event Form is photocopied and the original sent to the Coordinating Center to file in the participant charts. The photocopy should be filed in the participant's chart at the site. In the event of a serious adverse event, the study clinician takes any appropriate action to insure the safety of the participant (e.g., referral for evaluation or treatment).

Complete Medication Questionnaire

All participants complete a Medication Questionnaire (Form #17) between days 24 and 30 of each intervention feeding period. The questionnaire is designed to identify those individuals who start taking medications during the course of the study.

The questionnaire should be administered in an interview format, and all positive responses must be reviewed by a staff clinician. Individuals taking exclusionary medications must stop taking these medications. Completed questionnaires are entered on-site. Check the appropriate box on the Intervention Flow Form (#20) when this is completed

Assess Physical Activity Level

All participants must complete the Brief Physical Activity Questionnaire (Form #21) during days 24-30 of each intervention feeding period. Completed questionnaires are entered on-site within seven days of collection. Check the appropriate box on the Intervention Flow Form (#20) when this is completed.

Complete Anonymous Survey

All participants complete the Anonymous Survey (Form #25) between days 24 and 30 of each intervention feeding period describing their compliance during that period. The survey is to be handed out by the staff but has no identifying information on it. The participants are instructed to return it to a specific place or in a sealed envelope to ensure their anonymity. Check the appropriate box on the Intervention Flow Form (#20) when the form has been distributed to the participant. The competed forms are entered on-site.

Complete Diet Acceptability Survey

All participants complete the Diet Acceptability Survey (Form #35) twice during each feeding period, once between days 7 and 9 and once between days 27 and 30. Dietary staff administer the questionnaire and review returned questionnaires for completeness. Check the appropriate box on the Intervention Flow Form (#20) when the form has been completed. The competed forms are entered on-site.

Storage and Transmission of Lab Specimens

Urine and blood specimens collected during intervention feeding are stored locally until the end of the third intervention feeding period, at which time they are shipped to either the central lab or to long-term storage. Shipment must occur within two weeks of the end of the final intervention feeding period. Details for storage and shipment of specimens is found in Clinic MOP Chapter 12.

Activities Occurring Only Once During Intervention

Complete the Participation Survey

During days 24-30 of the third intervention feeding period, the participant is asked to complete the Participation Survey (Form #26). Check the appropriate box on the Intervention Flow Form (#20) when the form has been completed. The completed forms are entered on-site.

Exit Interview and Counseling

After all intervention feeding is concluded, participants receive a personalized Health Risk Assessment and nutritional counseling. This activity can happen in a group or individually. It does not need to coincide with the final day of feeding but may be incorporated into a celebration event. The associated activities are conducted primarily by the dietary staff. See Diet MOP Chapter 37 for more details.

Early Termination of Feeding

Inevitably, some participants will complete all required data collection, except for daily compliance monitoring, prior to the scheduled end of intervention feeding. Such subjects may be excused from further intervention feeding. This does not affect the timeline for data collection, however. Since final blood pressures must be taken on two of the final three days, intervention feeding cannot terminate prior to day 30. Participants who have not completed all required data collection cannot be excused early from feeding. Missed meals in such subjects count as noncompliance with the dietary requirements of the trial.

Premature Termination from Study

If for any reason a participant chooses to terminate from participation in DASH2 prior to the end of the cohort, complete the Premature Study Termination Form (#22). Collect as much of the study data as possible prior to the termination. See Clinic MOP Chapter 19 for details of closeout activities.

11. BLOOD PRESSURE ASSESSMENT 4

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Summary of Edits

Changes made in Version 1.1

- wording added regarding what to do if a technician is unable to get a valid reading

Changes made in Version 1.2

- The text on page 11-13 concerning recertification was modified to require only 4, instead of 15, measurements per month in order to stay certified. Certification lapses if this criteria is not met in 2 out of 3 consecutive months.
- A new para was added at the end of the section in "Monitoring for Digit Preference" (p 11-16) to note that the CC will periodically generate other blood pressure QC reports.
- Change in policy on sharing digit preference data?
- Clarified maintenance of Random-Zero and Conventional Sphygmomanometers section for bimonthly and quarterly maintenance and inspection.

Changes made in Version 1.3

- The rounding rules for the measurement of arm circumference were added.
- References to the DASH2 Certification system were added to the certification/re-certification sections.

Changes made in Version 1.4

- Changed references to timing of maintenance checks of equipment

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11. Blood Pressure Assessment

Overview

Correct measurement of blood pressure (BP) is of the utmost importance to the success of DASH2. It is essential that the procedures described in this chapter for measuring BP be followed exactly. Precision is essential for valid comparisons of blood pressure between groups of people and in individuals on different occasions.

In DASH2, sitting BP is measured using two readings with a random zero (RZ) sphygmomanometer. The essential distinction between the RZ and standard devices is a mechanism designed to produce a variable level of mercury in the mercury tube when the actual pressure in the cuff is zero. This is accomplished through an adjustable bellows chamber that is interconnected with the mercury reservoir at one end and the mercury tube at the other. The adjustment is made by the technician, who spins an external thumbwheel that contacts and rotates an internal, beveled cam; the position at which the cam comes to rest after spinning determines where the beveled edge will meet the movable diaphragm of the mercury chamber. When air pressure is applied through the cuff with the bellows cock in the open position, the diaphragm is displaced until it rests against the cam, and the mercury not accommodated by the new volume of the chamber is displaced into the mercury tube. The bellows cock, or valve, is controlled by the technician and locks the chamber system after the maximum inflation pressure desired has been applied, so that at the end of the reading, and only at the end, the mercury comes to rest at its "randomly" determined zero-pressure level. When this value is subtracted from the recorded readings the corrected readings give the corresponding true pressure levels. Thus, by adding this mechanism for varying the zero level of mercury, the RZ device obscures to the technician the true levels of pressure observed until after they have been read and the zero level subtracted. In this way, some of the recognized difficulties in technician performance are substantially reduced, particularly technician bias when readings fall near critical BP levels.

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

Equipment Required

Stethoscope

A standard, good quality stethoscope (e.g., Littman, HP) with a bell is used. Korotkoff sounds **are best heard with the bell** because of their low pitch frequency. Stethoscope tubing should be about 10-12 inches from the bell piece to the Y branching. This length provides optimal acoustic properties and allows the technician to read the sphygmomanometer at eye level in a comfortable position. Ear pieces should fit comfortably and snugly in the ears.

1. The ear pieces should be directed downward and forward into the external ear canal.
2. The ear pieces should fit tightly enough to exclude outside sound but not so tightly

that they cause discomfort.

3. The valve between the bell and the diaphragm should be turned in the correct direction.
4. The bell of the stethoscope should be placed lightly on the skin overlying the brachial artery. Light pressure accentuates low-pitched sound and avoids compression murmurs. Pressing too heavily with the stethoscope over the brachial artery causes turbulent flow in the artery and results in a murmur which may prolong the apparent duration of phase 4.

Sphygmomanometers

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

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

The RZ manometer has all the parts of the standard mercury device. In addition, it has a device built into the box-shaped back that changes the level of mercury in the calibrated glass tube. This device includes a second mercury reservoir area, the size of which can be changed to hold a larger or smaller amount of the mercury, thus allowing different amounts of mercury to remain in the calibrated glass tube and outside reservoir. The size of the second, inner reservoir is changed by turning a wheel on the side of the box. The second reservoir opens and closes with a bellows control valve on the face of the manometer.

All sphygmomanometers used in DASH2 should be sent to Hawksley for an overhaul prior to screening for cohort 1 if an overhaul has not been done in the prior year (i.e., since Summer 1996).

Cuffs

Proper cuff size is essential for accurate BP measurement. Clinical centers must have four standard cuffs available: small adult, regular adult, large adult, and thigh cuff. The cuffs used must be Baumanometer calibrated V-Lok cuffs with Baum brand bladders. The range markings on these and all commercial cuffs will overlap with the ranges DASH2 uses and do not offer a precise guideline. Therefore, all Baum cuffs used in DASH2 must be clearly marked on the inside surfaces with new range markings which correspond to the arm circumference ranges shown below for each cuff size.

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

The correctly determined cuff size used to record SV1 blood pressure should be the same cuff size used to record all of a participant's blood pressure measurements during screening. The arm circumference is measured to determine cuff size. Round all fractions up to the next whole number (i.e. 32.1 should be coded as 33). The rounded arm circumference is recorded on the SV1 Blood Pressure Form (#02). Because of the potential change in weight or body composition between screening and run-in, the arm circumference is measured again at the beginning of run-in and recorded on the Run-In Flow Form (#16). This allows the staff to determine the correct cuff size to be used during run-in and intervention.

Preparation for Blood Pressure Measurement

In relating to the DASH2 participants, remember that participation in the study is voluntary. Participants should be given a full explanation and instructions about the steps involved in BP measurement, as well as an opportunity to ask questions. Participants should be told in advance that their blood pressure readings will not be made available to them until the end of the study. However, they will be informed if their blood pressure exceeds the acceptable range. If a participant insists, a staff member may obtain an additional reading with a standard sphygmomanometer and inform him or her of the results. Because this may compromise the blinding of participants, this option should not be disclosed to participants in advance and should be used only if they insist on knowing their blood pressure.

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

Participants should be told <u>not</u> to engage in vigorous exercise, ingest food or caffeine, or smoke within a half hour of BP measurements. If a half hour has not elapsed, the BP measurements must be delayed until a half hour has passed.

Measurement Procedures

In DASH2, BP will be measured two times during each designated visit. It will take approximately 15 minutes to take the two readings, including an initial five-minute rest period. The BP measurements are obtained during the visit and prior to feeding.

Once the participant has had the procedures explained and the equipment has been checked, BP

measurement begins. The following steps must be followed precisely.

The right arm should always be used for the measurements. If the participant indicates that there is a medical reason for not having BP measured on his or her right arm (such as surgery, or if the right arm is missing), reverse chairs and proceed with the left arm. Write a note on the BP form indicating that the left arm has been used. If the participant seems particularly apprehensive about the procedure, delay wrapping the cuff until after the five-minute wait. Otherwise, check for correct cuff size by using the DASH2 markings on the baum cuff. If the index line falls on the maximum range markings, proceed to measure the arm circumference using the following procedure. Have participant stand erect holding the forearm horizontal at a 90^{o} angle. Arm length is measured using a measuring tape in metric units, measuring from the acromion or bony extremity of the shoulder girdle to the olecranon or tip of elbow. The midpoint is marked on the dorsal surface of the arm. Have participant relax their arm. With the participant's arm relaxed at their side, measure the arm circumference at the midpoint.

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

Palpate the brachial artery (just medial to and above the antecubital fossa) and mark this location for placement of the center of the bladder and stethoscope placement. Place the cuff on the right arm in the proper position. If the brachial artery is occluded by the cuff, as might happen with a very large but short arm, the participant is excluded from participating in DASH2. Indicate on the appropriate form (SV1 Blood Pressure Form (#2) or Run-In Flow Form (#16)) that you were unable to obtain a valid reading and note the reason.

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

After five minutes, take a 30-second pulse (radial artery) and record. Then connect the cuff to a standard mercury manometer to establish the pulse obliteration pressure. Palpate the radial pulse. Rapidly inflate the cuff to 80 mmHg and then slowly inflate it 10 mmHg at a time until the radial pulse can no longer be felt. Deflate and disconnect the cuff. Record the pulse obliteration pressure (POP).

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

If for any reason, you are unable to get a valid reading of the blood pressure on the participant, she is to be excluded from DASH2. Indicate on the SV1 Blood Pressure Form (#2) that you were not able to obtain a valid reading and note the reason.

Measurement # 1

Connect the cuff to the RZ manometer. Place ear pieces of the stethoscope in the ears with the tips down and forward. Open the bellows control valve and wait until the mercury settles. Using downstrokes only, turn the thumbwheel two or three times. NOTE: Do not spin the thumbwheel. Inflate rapidly but smoothly to the RZ peak inflation level. The eyes of the technician should be level with the mid-range of the manometer scale. Holding the pressure constant for five seconds with the bulb, close the bellows and control valve. Place the bell of the stethoscope on the brachial artery just below and not touching the cuff or tubing, and slowly deflate the cuff (2 mm per second) while listening. Record the first and fifth phases, reading the pressure in mmHg and rounding up to the nearest even number. The first sound heard in a series of at least two sounds is recorded for systolic BP (phase 1). For diastolic BP (phase 5), record the first silence in a series of at least two silences, NOT the last sound heard. After noting the DBP, continue to deflate at 2 mmHg per second until 10 mmHg below DPB, then rapidly deflate the cuff by opening the thumb valve. If there is an absent 5th phase (sounds heard to 00 mmHg), the beginning of the 4th phase should be used. Make a note if there is an absent 5th phase. Remove the stethoscope ear pieces. Disconnect the cuff and record the BP reading and the zero reading. **DO NOT SUBTRACT THE ZERO READING UNTIL BOTH MEASUREMENTS ARE COMPLETED.**

Measurement #2

After waiting 30 seconds with the participant's arm passively elevated for 5 seconds and on the table for 25 seconds, repeat as in measurement #1. After both readings are completed, the bellows control valve should be left in the OPEN position. If two identical consecutive zero readings are obtained, the maximum and minimum zeros should be checked before the device is used with another participant.

When finished recording the two RZ BP measurements, subtract the zero value from the reading to get the actual (corrected) systolic and diastolic values. Because of the importance of BP data in DASH2, all arithmetic must be done with a calculator after two readings have been completed. Be sure to perform these calculations away from the participant in order to keep them blinded to their readings.

Missing BP Information

If for any reason the technician is unable, or has forgotten, to complete any portion of this protocol and the participant has left this area, draw two horizontal lines through the relevant spaces on the data collection form. This is the correct way to indicate the missed information. If an entire reading is missed or is technically invalid and the participant is still in the clinic and has not yet eaten, a replacement reading should be obtained. Be sure to completely deflate the cuff and start over with a complete replacement reading. **Under NO other circumstances, however, may a replacement reading be obtained simply because the results seem unusual.** Always wait at least 30 seconds between readings.

Changing the Peak Inflation Level

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

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

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

Overview of Training and Certification

Personnel

All persons obtaining DASH2 RZ blood pressure measurements are required to undergo training and certification in RZ BP measurement technique by the study-wide trainer. Each clinical site designates two site-specific trainers. Each site will also designate an unlimited number of technicians.

Training and Certification

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

Introduction

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

The training strategy adopted by DASH2 is a two-stage blood pressure program. Before the program begins, each clinical center will identify two specific trainers for that clinic. These trainers from each clinical center will meet centrally in June 1997 for the first stage of training. The full training program will be presented at this time. The trainers who pass the program will be certified as Blood Pressure Trainers. The trainers can, in turn, train additional technicians in the clinical centers. This is the second stage of training. To this end, each center will be provided with the full set of training materials needed to reproduce the same program for their field and clinic staff. In this second stage, the Coordinating Center will receive documentation of each technician's training performance from the trainers in the clinical centers (including the successful completion of the written test [Form #51] and the Blood Pressure Certification Form [Form #52]). The sites will enter the technician's answers to the video exam (Form #58) into the BP certification module in the data entry/management application. The video test will immediately be scored and if the technician passed the exam, the rest of their certification results can be entered. If the technician does not pass the video test, they must re-take the test until they pass. After completion of data entry of the certification forms, the original exams should be copied and sent to the Coordinating Center for QC checks (attn: Reesa Laws). Various reports are available in the certification system. These reports can be generated at any time to identify who needs to be re-certified and when (see the Certification User's Manual for more details). Through this scheme, training will be the responsibility of both the clinical centers and the Coordinating Center will, in addition, remain responsible for overall monitoring and quality control.

Staff will be recertified according to the following schedule:

- All blood pressure trainers will receive their annual recertification during the DASH2 meeting in June. They will also need to be recertified locally at the six-month time interval.

- All blood pressure technicians are recertified by their local trainers during the breaks between cohorts (approximately every six months).

- All blood pressure technicians are required to meet these recertification deadlines unless they have been specially certified (e.g., new hires) during the three months prior to the start of the recertification window. If they have been certified for less than three months prior to this time they may wait for the following certification window before being recertified.

Steps Needed for Certification and Recertification

The first step is a series of blood pressure readings presented on a videotape to test the technician's identification of the systolic and diastolic Korotkoff sounds. The tape mimics the actual blood pressure measurement setting by providing a series of blood pressure readings which consist of both the visible falling of the mercury in a sphygmomanometer and the audible Korotkoff

sounds. A technician is certified if the criteria of the scoring procedure are successfully met. The criteria of the scoring procedure are not available to the clinical center or to the technicians. The scoring will occur after the entry of the technician's test sheets (Form #58) into the certification application (on the file server) is complete. The certification application will alert the data entry technician if the BP technician does not pass the video test (see the Certification User's Manual for more details).

- *Instructions for Taking the Videotest*. Viewing of the videotape, "Measuring Blood Pressure," may be done in a group or individually. The videotape consists of one practice reading followed by twelve systolic and diastolic sequences. After each sequence, the technician should record, on the recording sheet provided (Form #58), the systolic and diastolic reading for that sequence. All entries should be complete, legible, and written in black ink. The manometer in the videotape is read exactly as one would read in actual practice. Each blood pressure should be read rounded up to the nearest even digit. Each BP reading should agree within ±4 mmHg on any reading (systolic or diastolic), and averages should agree within ±3 mmHg.

The second step of blood pressure certification is the completion of the Blood Pressure Written Examination (Form # 51) after lectures have been presented. This is a short examination consisting of questions that test the blood pressure technician's knowledge and understanding of the measurement technique detailed in the training course. Technicians must score 100% on this exam. Scoring of the exam should be completed by the master trainer.

The third step is the successful completion of the Blood Pressure Certification Form (Form #52). The trainer is to verify the correct procedure for blood pressure measurement by observing the technician in one or more complete and uninterrupted exercises of the full procedure, in addition to three y-tubed readings with the trainer and technician recording blood pressure on three different individuals. When carried out without procedural errors, this record (Form #52) should be completed, signed, and included with the certification packet for the technician. Errors of procedure should be reviewed, discussed, and corrected until one completed determination is accomplished without error.

- *Y-Tube Stethoscope Observations.* Y-tube stethoscope observations are made for certification and recertification. The technician and trainer listen with the Y-tube and record the values on separate sheets (see Blood Pressure Certification Form #52). Two measurements on each of three subjects should be obtained. Readings by the trainer and technician should agree within ±4 mmHg on any reading (systolic or diastolic), and averages should agree within ±3 mmHg.

- *Observation of BP Measurement Procedures and Techniques*. All BP technicians must be checked to ensure that they are following procedures correctly and utilizing proper measurement techniques. This is necessary for both certification and recertification. If these measurements are made on a DASH2 study subject, the

observed blood pressure measurements for training may not be used for DASH2 data. The trainer uses the BP Observation Checklist (Form #53) to grade the technician while he or she follows the entire BP protocol to obtain two readings on a non-study or study individual, using a regular stethoscope. The trainer should be outside the immediate work area of the technician and should not make any comments during measurement. This part of the certification process should be done separately from the Y-tube certification.

After successfully completing the certification/re-certification, the completed forms need to be entered into the DASH2 Certification System (see the Certification User's Manual for details). As a means of maintaining a high level of quality and standardization over time, blood pressure technicians will be re-certified between cohorts (approximately every six months). The Coordinating Center will notify the clinical centers as to the schedule and requirements of the re-certification. A further description is in the section called Annual Recertification and Retraining.

Summary of Requirements for Blood Pressure Certification and Recertification

Certification

1. Attend DASH2 training session, or receive training from a certified DASH2 blood pressure trainer.
2. Read Blood Pressure Assessment (Chapter 19 of the MOP).
3. Successfully complete DASH2 blood pressure measurement technique and procedure. Record and submit results on DASH2 Blood Pressure Observation Checklist Form (Form #53).
4. Successfully complete three Y-tube stethoscope readings (average of three readings $\pm$4 of trainer measurements), using three different people, with DASH2 BP Trainer. Record and submit results on the Blood Pressure Certification Form (Form #52) .
5. Successfully complete the Blood Pressure Written Exam (Form #51) (100% correct).
6. Successfully complete 12 blood pressure examples on Videotape Test Sheet (Form #58) (100% correct).

Recertification

1. Required every six months for clinic staff and for DASH2 Blood Pressure Trainers. All trainers must be recertified either on site or centrally every six months. At least one trainer at each site must be recertified centrally on an annual basis.
2. Successfully complete DASH2 blood pressure measurement technique and procedure. Record and submit results on DASH2 Blood Pressure Observation Checklist Form (Form #53).
3. Successfully complete three Y-tube stethoscope and dual readings using three different subjects. Record and submit results on Blood Pressure Certification form (Form #52).
4. Successfully complete the Blood Pressure Written Exam (Form #51) on blood pres-

sure measurement (100% correct).
5. Successfully complete 12 blood pressure examples on Videotape Test Sheet (Form #58) (100% correct).
6. Must be actively taking blood pressure measurements using a random zero sphygmomanometer (at least 4 measurements per month). More than one violation of this criteria in any consecutive three month interval results in a lapse of certification.

Study Forms Required for Certification Procedures

Four study forms are required for certification.

1. Blood Pressure Written Examination (Form #51) and its key.
2. DASH2 Blood Pressure Observation Checklist Form (Form #53).
3. DASH2 Blood Pressure Certification Form (Form #52).
4. The Videotape Test Sheet (Form #58).

These four forms may be found in the Quality Control section of the DASH2 Forms Manual.

Blood Pressure Measurement Quality Control

Overview

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

In addition to these, DASH2 has adopted and instituted a comprehensive program to insure the collection of high quality blood pressure measurements. Factors contributing to this include:

1. Recruitment of the most qualified personnel.
2. Standardized training and certification.
3. Retraining of technicians having difficulties with standardized measurements.
4. Observations once every three months by the Blood Pressure Trainer of BP measurement techniques of the blood pressure technicians on either a participant or nonparticipant, using the Quarterly Checklist for Monitoring DASH2 Blood Pressure Observers (Form #50). One checklist is used for each blood pressure technician. These should be kept on file and will be reviewed at site visits.
5. Biannual (every six months) simultaneous Y-tube observations of each technician by the blood pressure Trainer on either a participant or nonparticipant (described in Bi-Annual Y-Tube Stethoscope Observations).
6. Frequent staff meetings to provide feedback.
7. Continuous editing and analysis of data by the Coordinating Center.
8. Presentation of data analysis to the clinical centers by the Coordinating Center to

provide feedback three times per year.

9. Equipment maintenance program (described in Local Blood Pressure Equipment Maintenance and Mercury Toxicity Safety Responsibility).

Monitoring for Digit Preference

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

NO TECHNICIAN SHOULD EVER HAVE A DIGIT PREFERENCE.

The Coordinating Center will provide monthly reports on digit preference of certified DASH2 blood pressure technicians. Because of the numbers of analyses, it is assumed that some of these reports will indicate "significant" digit preference by chance alone. Many others will serve as evidence of mild digit preference. Since there are five possible terminal digits for each blood pressure (0, 2, 4, 6, 8), the expectation of any large number of readings is that 20% of readings will end in each of those digits. For the purposes of responding to digit preference reports on individual technicians involving 30 or more blood pressure readings, the Coordinating Center will act as follows:

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

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

3. Statistically significant digit preference and one or more digits reported on 30-39% or 10-14% of readings: report to centers; center will share individual data and review technique with technician.

    - Statistically significant digit preference of this magnitude persists on next report: formal recertification must occur within one week of second report; observation and counseling should follow.
    - Statistically significant digit preference absent on next report and observed distribution includes no digits >29% or <16%: return to usual monitoring schedule.
    - Digit preference improved, but still statistically significant: review technique; monitor for continued digit preference; if significant on third consecutive report, regardless of range, recertification is required within one week of receipt of the third report. If more than one week elapses, the technician must cease taking DASH2 blood pressure measurements until such time as he or she is recertified.

4. Statistically significant digit preference; one or more digits reported $\geq$40% and/or $\leq$10% of the time and/or odd numbered terminal digits reported: Coordinating Center will notify PI/project director and discuss case individually; recertification required as soon as possible,

but in no case later than one week after notification.

In addition, the Coordinating Center will raise for discussion any situations that appear to be problematic for the trial. This might include individual technicians exhibiting extremes of digit preference or repeated, uncorrected levels of digit preference, or centers that collectively exhibit unusual levels of digit preference. The Steering Committee may take action specific to such cases at its discretion. Coordinating Center report on digit preference will reveal the specific digit that is biased.

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

Biannual Y-Tube Stethoscope Observations

Y-tube stethoscope observations are made in conjunction with the initial training and the bi-annual recertification. The trainer has the technician go through the entire blood pressure measurement procedure using the Quarterly Checklist for Monitoring DASH2 Blood Pressure Observers (Form #50). The technician and trainer listen with the Y-tube and record the value on separate sheets.

Two measurements on three subjects are obtained and originals sent to the Coordinating Center. A copy is kept on file at the clinical center.

It should be emphasized again that some difference (no more than average $\pm$4 mmHg in two readings on a single individual) between trainer and technician is to be expected, and that exact correspondence should not be expected nor taken even implicitly as a criterion of accurate performance by the technician. Rather, this process is intended to formalize the "live reading," to provide a written record of the results, and to identify gross problems that could be detected only by the trainer's close involvement with the blood pressure technician. Any problems identified by the trainer or raised by the technician should be discussed and, as far as possible, resolved.

Responsibilities of the Coordinating Center and the BP Trainers

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

Each site is required to have at least two certified trainers. If, between recertifications, the Coordinating Center and/or a trainer has evidence that a problem may exist with a technician, the three parties will discuss the matter. It may be necessary for the Coordinating Center to temporarily rescind a certification and for the clinical center to retrain the technician. In this case,

until the technician is recertified, he or she may not take blood pressure measurements for DASH2.

It is also the responsibility of the Coordinating Center to monitor the specific activities of the BP trainers. In addition to the continuous monitoring of all incoming blood pressure data (e.g., for digit preference or bad values), the files of the biannual blood pressure checklists and maintenance logs (Forms 50, 54-57) will be reviewed at each site visit for completeness and accuracy. Finally, the trainers themselves will be recertified centrally every summer, before the annual recertification of the other blood pressure technicians.

Maintenance of Random-Zero and Conventional Sphygmomanometers

Introduction

Each clinical center is responsible for the proper operation and maintenance of its BP equipment. Responsibility for proper maintenance is assumed by the clinic coordinator or designated person, and all staff are instructed to report promptly any real or suspected equipment problems to that person. All checks, inspections, and cleanings are documented and recorded by date in a permanent log maintained separately for each unit. All maintenance logs (Forms #54-57) and biannual checklists (Form #50) should be stored in the permanent log binder. Problems and solutions are also recorded there. Logs will be reviewed by CC staff at periodic site visits and the CC will periodically make requests for copies of these documents for quality control checks.

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

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

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

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

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The Standard and RZ manometer and cuffs should be thoroughly inspected and cleaned (if necessary) biannually. The inspection should include the following:

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

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The equipment should be cleaned if inspection indicates that cleaning is necessary, or at least once per year. In addition, every three months the accuracy of the RZ device should be checked using a standard manometer and a Y-tube and RZ zero levels should be checked.

Safety Responsibility

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

General Guidelines

1. The objective of maintenance of all sphygmomanometers is to ensure their accuracy for blood pressure measurement. The manometer column must be clean and the system free of mercury leakage. The zero level for the conventional device should be accurately read as 0 mmHg at the top of the mercury meniscus. The “zero” levels for the random-zero (RZ) device should have a range of approximately 20 mmHg between the maximum and the minimum “zero” level. These values should remain constant for a given instrument, and the maximum “zero” for each instrument should be indicated by a label on the front of the machine itself, for comparison to zero levels obtained during actual readings taken with the device.
2. These devices should be cleaned and checked thoroughly on a quarterly basis or approximately every three months. ~~More frequent~~Monthly inspections should be made to ensure there has been no mercury spillage or leakage and no obvious malfunction of the device. Instruments used in clinics should be inspected ~~weekly~~monthly. Those inspections should include a check of ~~zero levels~~, mercury leakage, operation of valves, manometer columns for dirt or mercury oxide deposit, and

condition of all tubing and fittings.

3. Procedures for inspecting the RZ Manometer (RZM) are outlined below. The manometer portions of both instruments are produced by W. A. Baum Company (Copiague, New York 11726), so that maintenance for this portion of the two devices is the same, as is the case for cuffs, bulbs, and air control valves. More detailed instructions covering these parts are provided in the Baumanometer Service Manual, which is available from the W. A. Baum Company.
4. **Work area and mercury spillage.** All blood pressure devices used in DASH2 contain mercury, which is a volatile metal at room temperature. In view of the problem of spillage and retrieval of this material, a definite work area should be designated for all manipulations. This area should be in a well-ventilated room. Rugs should not be present. The work bench should be a flat, smooth surface which can be easily cleaned, with adequate space. All work should be done in a large tray or basin with edges that will contain any mercury spill that may inadvertently occur in the process of maintaining the machines. A mercury cleaning solution which inactivates elemental mercury and prevents it from vaporizing should be kept in stock in the work area and the person doing the work should wear gloves and a lab coat with no pockets and should remove rings, watches or other metallic objects from his/her hands. A procedure should also be developed for proper handling of accidental mercury spills and all staff made aware of those procedure.

Common Problems with—and Solution for—both Manometers

Dirty manometer column

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

Mercury leakage

This can be due to any of the following:

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

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

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

Inspection of the Random-Zero Manometer

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

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

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

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

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

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

5. Verify the maximum "zero" obtainable

- The bellows valve should be in the "OPEN" position, and no pressure should be in the cuff. The cam should rotate freely.
- Set the cam manually in such a position that the level on the end of the cam will contact the moving wall of the chamber after the shortest possible displacement of this wall toward the cam. (This position draws the least mercury into the reservoir and

produces the highest "zero" level for the amount of mercury in the device at this time.)
- Inflate the cuff above 200 mmHg and maintain it at this pressure until the chamber wall has come to rest against the bevel of the cam.
- Turn the valve to "CLOSE," wait a full five seconds, and deflate and disconnect the cuff.
- Record the zero level. It should compare closely (within 4 mmHg) with the value on the label that was placed on the face of the manometer by the trainer.

6. Verify the minimum "zero" obtainable

- Repeat exactly as for (5) above, except set the cam so that the moving wall of the reservoir will move its maximum distance before contacting the cam. (This position draws the most mercury into the reservoir and produce the lowest "zero" level for the amount of mercury in the device at this time.)
- Ensure that full pressure in the cuff is maintained until the wall of the chamber comes to rest against the bevel of the cam; this may take several seconds.
- Turn the bellows valves to "CLOSE," and deflate and disconnect the cuff.
- Record this "zero" level; it should compare closely ($\pm$2 mmHg) with the value determined when the machine was calibrated.

7. Adjust zero levels if needed

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

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

If the minimum zero level is below 0:

- Open the bellows control valve and the valve at the top of the mercury reservoir, unscrew and remove the knurled cap at the top of the manometer column, and remove the air bleed screw at the top of the bellows chamber.
- Pour clean mercury into the top of the manometer tube, using a hypodermic syringe barrel or tight paper cone as a funnel. (As Baum writes, mercury can be cleaned of floating dirt and oxides by pouring it through a rolled cone of ordinary scratch paper with a pinhole at its apex. Note that some mercury will stick on and in the paper, so handle with care). About 400 grams (or 14 ounces) of mercury are needed to fill an

instrument for a zero range of near 10 to 30 mm.

- Firmly screw the knurled cap onto the top of the manometer column, and apply pressure to the mercury reservoir until the mercury rises into the vertical air column at the top of the bellows chamber. Tighten the air bleed screw quickly and firmly, while the mercury is a short distance into the vertical air column.
- Apply enough additional pressure to raise the mercury to near the top of the manometer column (if it is not already that high); then release the pressure, thus to collect mercury droplets and clear the column of air bubbles. There are likely to be air bubbles trapped on the walls of the plastic tube at the bottom rear; these can sometimes be removed by tapping the tube sharply, but they are, at any rate, of no consequence.
- Determine zero range and adjust as needed.

b. If the maximum zero level is greater than 4:

- Unscrew and remove the knurled cap from the top of the manometer column. Using a syringe with a small tube, such as a catheter, remove the mercury from the manometer. (Or, if these are unavailable, pour surplus mercury from the open manometer column. See Baum instructions; be sure that the mercury reservoir valve is closed before inverting the manometer to pour the mercury out.)

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

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

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

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

- Set the cylindrical cam for maximum bellows volume, and open the bellows control valve.
- Raise the reservoir pressure to about 280.

- Close the bellows valve and release pressure on the reservoir.
- Tilt the RZM to the right (reservoir on down side) until all mercury has disappeared below the manometer column. Close the reservoir valve (handle to front). Rest the RZM on its right side, with the spin wheel above the table surface.
- The manometer column may now be removed.

10. Maintenance requirements are minimal, but essential.

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

For BP Trainers Use Only

Procedures for Training and Certifying BP Technicians—For Trainers' Use Only

When the trainer feels that the technician has reached a satisfactory level of proficiency in determining the systolic and diastolic blood pressure level, the technician should be given the Blood Pressure Certification Test (Form #52). The technician must demonstrate to the trainer one or more complete and correct blood pressure determination procedures for 1) cuff selection by correct arm measurement, 2) palpating the brachial artery to center the cuff, 3) proper placement of the cuff with the center of the bladder over the brachial artery, 4) determination of peak inflation level using the random-zero sphygmomanometer, and 5) correct blood pressure measurement following the protocol. The final test to certify a technician will be a videotape test (Form #58). The test involves watching a mercury column on a sphygmomanometer and listening to the simultaneous Korotkoff sounds during blood pressure levels for each on the videotape test sheet. The sheet is then sent to the Coordinating Center where it is graded "pass" or "fail." The systolic and diastolic readings are entered into a computer and scored.

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

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

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

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

Trainers in the Clinical Center

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

Preparation for Trainers

Gather all the blood pressure equipment:

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

Familiarize yourself with all the blood pressure equipment. Prepare for mercury safety procedures and prepare an equipment maintenance schedule. Check all random-zero sphygmomanometers for maximum and minimum zero levels. The standard sphygmomanometers should be checked so that the top of the mercury meniscus is at the zero marking. The stethoscopes should be clean and turned to the bell. The cuffs and air valve should be checked for air leaks.

Gather all the Training Materials

- This training manual
- Blood Pressure Written Exam and answer key (Form #51)
- Blood Pressure Certification Form (Form #52)
- Blood Pressure Observation Checklist (Form #53)
- Videotape Exam (Form #58)
- 2x2 slide projector and carousel
- Videotape machine
- Black ball-point pen
- Slides and videotape

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

Training Tips

- Schedule the training sessions over a period of days. An unhurried schedule gives the technician a chance to absorb and demonstrate the procedures and knowledge with more confidence. Remember, you may be training someone who needs to unlearn previously learned blood pressure procedures. Also remember the stethoscope can cause ear discomfort when used for several hours at one time.
- Try to keep the group size workable. The lectures may work for a large group, but consider the waiting/noise factor when scheduling the written test, blood pressure practice/evaluation, and the videotape viewing.
- The certification of the technician and duties as a technician should not be planned

for the same day. The technician cannot complete the certification and begin taking participant blood pressures that same day. Plan time to allow for entry of the written exam (Form #51), the video exam (Form #58) into the data entry/management application, and generation of the notice of certification from the application.

Documentation of Certification

- Each person in the clinical center that will be filling out any part of a blood pressure form will need a staff ID code. This includes the blood pressure technicians. Only one code number should ever be assigned to one person, no matter how many changes in status might occur.
- The Written Examination (Form #51) should be taken by the technician and graded by the trainer. If there are any differences in responses, it should be discussed and clarified. The trainer should indicate those responses that were discussed by initializing them.
- The Blood Pressure Certification Form (Form #52) should be carefully followed to ascertain that the technician has a clear understanding of the procedures. This evaluation should be completed by the trainer as a passive observer. Avoid prompting the technician. The technician should complete one or more complete and uninterrupted exercises of the full procedure. Errors of procedure should be reviewed, discussed, and corrected. When carried out without procedural errors, this record should be completed, signed, and included with the certification packet of the technician.
- When the videotape test (Form #58) is taken, remind the technician to insert leading zeros where necessary and to complete the entire form. The test will be graded upon entry into the data entry/management application on the DASH2 file server. If a systematic problem is discovered via computer scoring, the Coordinating Center will instruct you as to the type of problem discovered. The specific problem would not be identified to the technician, as this may artificially bias the technician's responses. Retraining, possibly by Y-tube readings, may help to identify and correct the problem. If the problem is not corrected within several retrainings, the problem is probably auditory and technician would need to be hearing tested and, if correction is not possible, excluded from taking blood pressures. If a hearing correction is possible, the technician will need to be retested. The Coordinating Center needs to have complete documentation of the certification. We suggest the trainer keep the originals and send photocopies to the Coordinating Center. The Coordinating Center will instruct the trainer when recertification should be scheduled, on a biannual basis.

Lecture #1—Blood Pressure Measurement—Problems and Solutions

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

methods learned through this training program are carried out.

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

The start of this century was the period when current, indirect methods were introduced. These were more practical than the lethal method of Hales and qualify as what we would term today a "non-invasive" technique. This indirect method, now almost universally employed, combines the work of Riva-Rocci, an Italian physician who developed the inflatable cuff, and Korotkoff, the Russian physician who described his auscultatory findings, heard through a stethoscope placed over the brachial artery, as an improvement over mere palpation of the radial pulse, a technique limited to detecting systolic pressure alone.

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

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

Discussion of blood pressure in these terms would be seriously incomplete, however, if we did

not take account of the fact that important problems of measurement exist. It is imperative that these problems be recognized and, as far as possible, overcome. What are they?

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

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

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

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

Training in blood pressure measurement will take three forms. First, there will be lecture and slide presentations to acquaint you with the proper procedures for measuring blood pressure and

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

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

Lecture #2—The Random-Zero Device

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

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

Slide# Script for Slide

1. As we have already discussed, the random-zero device and the conventional mercury sphygmomanometer are essentially very similar. This can be seen in comparing the two devices side by side. The random-zero device is unique, however, as the following slides will show.
2. The crucial distinction is the wheel on the righthand side of the random-zero casing. To get a little closer to the workings of the device, we may remove the front of the casing.
3. The manometer column, the cuff and its connections, and one notable feature: a lever

controlling the reservoir outlet. This lever is always closed (i.e., turned to the left) for carrying the device and opened (i.e., turned to the right) for operating it. You might notice also that the mercury rests at a level well above 0 mm, even though the cuff is not inflated. Let's take a close look at the mechanism, that accomplishes this to see how simple it really is.

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

Lecture #3—Procedures in Blood Pressure Recording

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

Coordinating Center). Listed below is the script to accompany each slide.

Slide# Script for Slide

Equipment and Supplies (Slides 1-11)
Arm Measurement (Slides 12-21)
Preparation for Actual Readings (Sides 22-27)
Pulse (Slides 28-37)
First Blood Pressure Reading (Slides 38-49)
Between Readings (Slide 50)
Second and Third Blood Pressure Reading (Slides 51-53)

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

forearm horizontal.

15. Arm length is measured from the acromion or bony extremity of the shoulder girdle,
16. To the olecranon, or tip of the elbow.
17. The full arm length from acromion to olecranon is measured, and
18. The midpoint is marked on the dorsal surface of the arm.
19. With the participant's arm relaxed at the side, the arm circumference is measured by drawing the tape snugly (without indenting the skin) around the arm at the level of the midpoint marking. Care must be taken to keep the tape horizontal.
20. The chart of arm circumference measurements and corresponding cuff sizes is consulted, and
21. The proper cuff size is checked. Indicate the cuff size on the form.
22. The participate should then be seated with the elbow and forearm resting comfortably on a table with the palm of the hand turned upward. The area to which the cuff must be applied must be bare. The bend of the elbow should be at heart level.
23. Legs should be uncrossed and feet comfortably flat on the floor.
24. The brachial artery is located by palpation and marked (just medial to and above the antecubital fossa).
25. As is the midpoint of the rubber bladder within the cuff. Often this point is marked on the cuff itself.
26. The cuff is then wrapped about the arm so that the midpoint of the bladder lies over the brachial artery, and the mid-height of the cuff is at heart level.
27. Allow a five minute wait before taking the BP. Conversation should be limited during this time. You should leave the room after a brief explanation.
28. After the period of 5 minutes at rest has been completed, the radial pulse is counted for a timed interval of exactly 30 seconds.
29. The 30-second count is recorded.
30. The standard mercury sphygmomanometer is then connected with the cuff.
31. The manometer is positioned so that the midpoint of the column is at the technician’s eye level when in position to carry out the measurement of blood pressure.
32. The radial pulse is located, and palpated.
33. The cuff is inflated quickly to 80 mmHg.
34. Slowly inflate at 10 mmHg at a time until the radial pulse can no longer be felt.
35. The cuff is quickly and completely deflated.
36. Record the pulse obliteration pressure (POP).
37. Calculate and record the peak inflation level (pulse obliteration pressure + 60). The peak

inflation level used for BP measurement must be >180 mmHg.

38. To perform the measurement of blood pressure itself, the brachial artery is again palpated. Note that the arm remains bare.
39. The wheel of the random-zero is gently spun with the valve in the OPEN position.
40. The stethoscope ear pieces are put in place with the ear pieces positioned forward.
41. The bell of the stethoscope is placed carefully and without excessive pressure over the brachial artery, just between the elbow crease and lower edge of the cuff.
42. With the valve still in the OPEN position, the cuff is inflated quickly and smoothly to the peak inflation level or to 180 mmHg, whichever is higher. Hold the mercury at this pressure for five seconds.
43. The valve is then turned to the CLOSE position.
44. The cuff is then deflated very steadily at 2 mmHg per second,
45. To a level 10 mmHg lower than the level of the last Korotkoff sound heard.
46. The mercury level is now dropped quickly to the "zero" level for this reading.
47. The observed values for the SBP, DBP, and "zero" values are recorded.
48. Remove stethoscope ear pieces.
49. Disconnect the cuff and record the zero reading. DO NOT SUBTRACT THE ZERO READING UNTIL ALL THREE MEASUREMENTS ARE COMPLETED.
50. Have participant raise arm for five seconds, then rest arm on table for 25 seconds.
51. The second and third readings are carried out exactly as the first.
52. After finishing both RZ BP measurements subtract the zero value from the readings to get the actual systolic and diastolic values.
53. All arithmetic must be done with a calculator after both readings have been completed.

Lecture #4—Equipment Maintenance and Mercury Toxicity Safety

(This lecture is essentially a repeat of the material covered under pages 15-20).

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

General Guidelines

1. The objective of maintenance of all sphygmomanometers is to ensure their accuracy for blood pressure measurement. The manometer column must be clean and the system free of mercury leakage. The zero level for the conventional device should be accurately read as 0 mmHg at the top of the mercury meniscus. The "zero" levels for the random-zero (RZ) device should have a range of approximately 20 mmHg between the maximum and the minimum "zero" level. These values should remain constant for a given instrument, and the maximum "zero" for each instrument should be indicated by a label on the front of the machine itself, for comparison to zero levels obtained during actual readings taken with the device.
2. These devices should be cleaned and checked thoroughly on a biannual basis or approximately every six months. More frequent inspections should be made to ensure there has been no mercury spillage or leakage and no obvious malfunction of the device. Instruments used in clinics should be inspected weekly. Those inspections should include a check of zero levels, mercury leakage, operation of valves, manometer columns for dirt or mercury oxide deposit, and condition of all tubing and fittings.
3. If your biannual check and bimonthly fall in the same month complete both maintenance logs.
4. Procedures for inspecting the RZ Manometer (RZM) are outlined below. The manometer portions of both instruments are produced by W. A. Baum Company (Copiague, New York 11726), so that maintenance for this portion of the two devices is the same, as is the case for cuffs, bulbs, and air control valves. More detailed instructions covering these parts are provided in the Baumanometer Service Manual, which is available from the W. A. Baum Company.

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5. **Work area and mercury spillage.** All blood pressure devices used in DASH2 contain mercury, which is a volatile metal at room temperature. In view of the problem of spillage and retrieval of this material, a definite work area should be designated for all manipulations. This area should be in a well-ventilated room. Rugs should not be present. The work bench should be a flat, smooth surface which can be easily cleaned, with adequate space. All work should be done in a large tray or basin with edges that will contain any mercury spill that may inadvertently occur in the process of maintaining the machines. A mercury cleaning solution which inactivates elemental mercury and prevents it from vaporizing should be kept in stock in the work area and the person doing the work should wear a lab coat with no pockets and should remove rings, watches or other metallic objects from his/her hands. A procedure should also be developed for proper handling of accidental mercury spills and all staff made aware of the procedure.

Common Problems with—and Solution for—both Manometers

Dirty manometer column

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

Mercury leakage

This can be due to any of the following:

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

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

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

Inspection of the Random-Zero Manometer

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

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

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

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

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

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

5. Verify the maximum "zero" obtainable

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

6. Verify the minimum "zero" obtainable

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

- Turn the bellows valves to "CLOSE," and deflate and disconnect the cuff.
- Record this "zero" level; it should compare closely (+2 mmHg) with the value determined when the machine was calibrated.

7. Adjust zero levels if needed

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

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

If the minimum zero level is below 0:

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

If the maximum zero level is greater than 4:

- Unscrew and remove the knurled cap from the top of the manometer column. Using a

syringe with a small tube, such as a catheter, remove the mercury from the manometer. (Or, if these are unavailable, pour surplus mercury from the open manometer column. See Baum instructions; be sure that the mercury reservoir valve is closed before inverting the manometer to pour the mercury out.)

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

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

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

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

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

10. Maintenance requirements are minimal, but essential.

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

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Summary of Edits

New changes in version 1.1

- Added references to two new forms for tracking the specimens. The Central Lab Shipping Logs for Urine and Bloods are referenced in the forms on the file server section, the preparing for the visit section, the preparing/storing the shipping supplies, the process and storing section, the data entry section and the shipping to CLCS section.
- Updated collection of blood samples section with information about the order of blood draws.
- Updated the data entry and shipping to CLCS sections with the final procedures for data management.

New changes in version 1.2

- Updated Process and Store Specimens, EDTA Plasma. Expands description of buffy coat, including addition of diagram. Specifies to collect buffy coat at SV3 visit.
- Updated contact/shipping sections with references to the storage repository, McKesson BioServices.
- Updated plasma processing. Specimens should be spun at room temperature not in a refrigerated centrifuge. Also two samples of renin will be collected instead of one.
- Updated the data entry/data management section and the shipping to CLCS section with the now final procedures. Note: this is a big change from version 1.1.

New changes in version 1.3

- Clarified type of REVCO freezer to have available
- Changed references to number of renins to collect as 2 instead of 1
- Modified section on disposal of materials
- Added temperature information on renin collection to collection of blood samples section
- Clarified wording on urine collection section

New changes in version 1.4

- Clarified tube labeling section: write in draw date or urine collection start date

New changes in version 1.5

- Changed all references from MBS to BBI (the new storage lab)
- Modified 24 hour urine collection participant instructions (appendix)
- Added a bullet to the collection of urine sample section specifying which dates are preferable to begin collection
- Changed lab tracking section to reflect changes to the lab tracking system

12. Central Laboratory Procedures

Introduction

The Core Laboratory for Clinical Studies (CLCS) of Washington University Medical School will serve as the central laboratory for DASH2. BBI – Biotech Research Laboratories will serve as the repository for the DASH2 storage specimens. This manual contains the information needed to collect, process, and ship specimens to the laboratory for analysis and the repository for storage. Please review the manual before the beginning of the study and contact the laboratory or the repository if you have any questions or require additional information.

Contacts at CLCS

Customer Service	(314) 362-3522
Laboratory Fax Number	(314) 362-4782
Laboratory Director Thomas Cole, Ph.D.	(314) 362-3516
Laboratory Manager Connie Ferguson, M.T. (ASCP)	(314) 362-4625
Clinical Studies Coordinator Julie McDowell, M.T. (ASCP)	(314) 362-4625
Information Systems Supervisor Dave Gibson	(314) 362-7869
Technical Supervisor Mike Macke, M.T. (ASCP)	(314) 362-4671

U.S. Mail Address:

Thomas Cole, Ph.D.
Washington University School
of Medicine
660 S. Euclid Ave., Box 8046
St. Louis, MO 63110

Shipping Address: (UPS & FedEx)

Core Laboratory for Clinical Studies
Dave Gibson/Core Laboratory
Washington University School
of Medicine
499 S. Euclid Ave.
St. Louis, MO 63110

Contacts at BBI

Principal Investigator Dr. Mark Cosentino	(301) 208-8100
Laboratory Manager Alfred Chun	(301) 208-8100 (301) 208-8829 fax

Shipping address: (UPS & FedEx)

Alfred Chun
BBI – Biotech Research Laboratories
217 Perry Parkway
Gaithersburg, MD 20877

Study/Supplies

The following will be provided by the CLSC before screening begins:

- · Blood collection tubes
- · Labels and vials for specimen aliquots
- · Shipping and storage boxes for specimens
- · 25 urine collection hats and 30 jugs
- · 30 blood collection kits for Visits SV3, IFP/I, IFP/II and IFP/III
- · Shipping containers and supplies
- · Pre-addressed Federal Express Airbills
- · Disposable transfer pipettes

The CLCS will distribute specimen collection kits directly to each center as needed. These shipments require about three days shipping time. 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. Requests for supplies can be made by telephone, fax, or by enclosing the order form with your shipment to the CLCS. The Request for Additional Lab Supplies (Form #89) is found on the DASH2 File Server. Each center will be responsible for maintaining an adequate inventory of supplies. **Please call CLCS at least 7 days before your Lab Supplies run out.**

The CLCS will also provide the collection kits for the storage specimens. The BBI will provide the shipping container and supplies. The CC will contact the BBI after randomization to inform the repository of the number of specimens to expect from each site so they can send the correct number of shipping containers.

The following are found on the DASH2 File Server:

- Central Laboratory Operations Manual (Clinical MOP, Chapter 12)
- 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. Renin specimens are stable for only 30 days. Contact the CLCS if you do not have access to a -70°C freezer.
- Dry ice for shipping
- Federal Express pick-up or drop-off service
- Racks for tubes
- Phlebotomy supplies
- Distilled or de-ionized water
- Indelible markers for labels
- Biological waste bags
- 6 N HCl preservative for urine
- 2 L graduated cylinder for measuring urine volume
- Graduated pipettes for aliquoting urine

Preparing for the Visit:

Materials Needed

- Visit-specific kits (see description below)
- Visit and participant specific labels
- Central Lab Collection Form- 24-Hour Urine (Form #30)
- Central Lab Collection Form- Fasting Blood (Form #31)
- Central Lab Shipping Log - Urine (Form #38)
- Central Lab Shipping Log - Blood (Form #39)

Description of Visit Kits used for Blood Draws

A single kit of blood collection supplies will be used for all visits (SV3, IFP/I, IFP/II and IFP/III). Labels will be sent separately for each visit.

Supplies

1 needle
Transfer pipettes (bulk supplies)

Plasma tubes required

2 x 10 mL EDTA Vacutainer tubes (purple top)
1 x 13 mL plastic pooling vial (purple dot)
3 x 2 mL plastic freezing vials (clear top)
2 x 2 mL plastic freezing vials (purple top for renin or buffy coat)

Serum tubes required

2 x 10 mL SST Vacutainer tubes (red/gray top)
1 x 13 mL pooling vial (red dot)
4 x 2 mL plastic freezing vials (red top)

Description of Visit Kits used for Urine Collection

Urine collection hats and jugs will be provided in bulk for distribution at visits SV2, IFP/I, IFP/II, and IFP/III. Labels will be sent separately for each visit.

Supplies

24-hour urine collection jug
6 x 8 mL plastic freezing vials (yellow dot)
Packet of labels for participants

Prepare the Labels

1. Labels are provided for all tubes and vials. Blank specimen identification labels are provided for urine at SV2 and for bloods at SV3. Labels will be pre-printed with participant's identification number for all intervention visits and will be sent to the clinical sites from the CLCS separately from the kits.

2. At SV3, for all labels:
   Record the subject's unique 10-digit identification code.
   Record the draw date of the visit or urine collection start date.

3. At each intervention visit, all information will be pre-printed except for the draw date, which is recorded at the time of the visit.

4. Affix the completed labels to the appropriate tubes found in the kit before 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, and that the writing be legible.

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 CLCS and BBI four times during each cohort. The SV3 shipment will go out at the end of run-in and the intervention shipments will go out at the end of each of the three intervention periods. Contact the laboratory and the repository prior to shipping.

2. You will need to store the specimens in racks in the freezer until you are ready to send a shipment to CLCS or to storage. Complete the Central Lab Shipping log forms (form #38 and #39) when collecting the sample in order to record which sample is going into the slots in the freezer boxes. These forms are for internal use only. They will not be entered into the data entry system. See directions below for shipping the specimens.

At the Visit:

General Instructions

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

Collection of Blood Samples

- A fasting blood must be collected between SV3 and the start of Run-in feeding and during days 22-30 of each intervention feeding period. Subjects must have fasted 8-14 hours prior to blood collection, with only water allowed. If the subject has not been fasting, the visit must be rescheduled. Additionally, the participant must have been in an upright position (defined as seated or standing) for at least 1.5 hours prior to the blood draw.

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

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

- Draw the two SST serum tubes before the two 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 renin specimen must be kept at room temperature through all stages up to the point the plasma sample is aliquotted into the storage tube and then immediately frozen. The specimen can sit out at room temperature for no more than 30 minutes after collection before it needs to be spun and processed.

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

Collection of Urine Sample

- At SV2 and between days 22-30 of each Intervention Feeding Period, 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. Make sure that a label is affixed to the collection jug and that it is filled out 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. Also confirm that the participant: voided her bladder at the start of collection and did not save the specimen, collected a final voiding at the end of the collection period, and returned the specimen within 24 hours of the final voiding.

- The specimen is considered to be inadequate if any of the following are true.

    - The total duration of the collection is less than 22 hours or greater than 26 hours
    - The collection period did not start with an initial, discarded voiding
    - More than one voiding (including the final voiding) was missed
    - The total volume of the sample is less than 500 cc
    - The urine is collected during menstruation

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

Serum

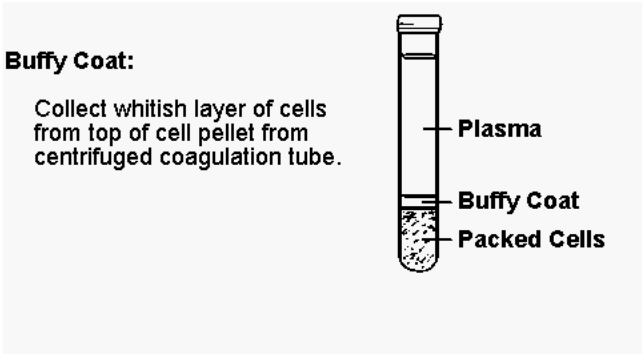
1. Allow the 2 x 10 mL SST tubes (red/gray top) to clot for 30-60 minutes at room temperature in an upright position. Verify that the specimen is fully clotted.
2. Centrifuge the clotted tubes for 15 minutes at 1,500 x g. After centrifugation, check the SST tubes for a complete gel barrier between the serum and the cells. Re-centrifuge if the barrier is incomplete or if red cells are seen above the barrier.
3. Pour the serum from the SST tubes into the 13 mL pooling vial. Cap the pooling vial and invert several times to obtain a homogeneous specimen.
4. Using a transfer pipette, transfer the serum from the 13 mL pooling vial into 3 x 2 mL freezing vials with red caps, labeled for 'Storage' and 1 x 2 mL freezing vial with red cap labeled for 'Lipids.'
5. Fasten the appropriately colored caps tightly and immediately place the vials in freezer racks at -70oC.
6. Fill out Central Lab Shipping Log - Blood (Form #39) as you fill the slots in the box.
7. Fill out the worksheet for the Central Lab Collection Form- Fasting Blood (Form #31)
8. If a repeat draw is necessary, repeat the steps above.
9. After any repeat draws for this participant are complete, use the worksheet to complete Form #31

EDTA Plasma

1. Centrifuge the 2 x 10 mL (purple top) EDTA tubes without delay at room temperature. Centrifuge at >1,500 x g for 15 minutes to remove blood cells. No red cells should be present in the plasma or along the sides of the tubes.
2. Using a transfer pipette, transfer the plasma into the 13 mL plastic pooling vial. Cap the pooling vial and invert several times to obtain a homogeneous specimen.
3. Using transfer pipettes, transfer the plasma from the pooling vial into the following freezing vials:

At SV3 Visit:

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



  Collect the buffy coats from both EDTA tubes and transfer into the 2 mL freezing vial with a purple cap labeled for "Buffy Coat."

- Transfer 1.5 mL plasma into 3 x 2 mL freezing vials with clear caps labeled for 'Storage.'

  Between Days 22-30 of each Intervention Feeding Period:

- Transfer 1.5 mL plasma into 3 x 2 mL freezing vials with clear caps labeled for 'Storage.'
- Transfer 1.5 mL plasma into 2 x 2 mL freezing vials with a purple cap labeled for 'Renin.'

4. Fasten the appropriately colored caps tightly and immediately place the vials in freezer racks at -70oC.
5. Fill out Central Lab Shipping Log - Blood (Form #39) as you fill the slots in the rack.
6. Fill out the worksheet for the Central Lab Collection Form- Fasting Blood (Form #31).
7. If a repeat draw is necessary, repeat the steps above.
8. After any repeat draws for this participant are complete, use the worksheet to complete Form #31.

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 (use a graduated cylinder). Note the volume on Form #30.
4. Label and prepare 6 x 8 mL freezing vials as follows:
   Tubes 1, 2, and 3: Add nothing to the vials labeled 'NO HCl".
   Tubes 4, 5, and 6: Add 2 drops of 6 N HCl to the vials labeled 'With HCl'.
5. Add 5 mL of well-mixed urine to tubes 1-6, using a graduated pipette. Cap securely. Invert to mix.
6. Fasten the yellow dot caps tightly and immediately place the vials in freezer racks (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.
6. Fill out Central Lab Shipping Log - Urine (Form #38) as you fill the slots in the box.
7. Fill out the worksheet for the Central Lab Collection Form- 24-hour Urine (Form #30).
8. If a repeat collection is necessary, repeat the steps above.
9. After any repeat collections for this participant are complete, use the worksheet to complete Form #30.

Data Entry/Data Management

In order to be able to send the shipment to CLCS or to BBI, you must send the completed Forms 30 and 31 to the data entry technician to be entered. When you are ready to ship, print out the Central Lab Data Completeness Report (#35) from the DASH2 Data Management System (see monitoring reports) to see if there are any additional forms you need to enter. All Central Lab Collection forms for a particular visit should be entered before preparing boxes for shipment. All audits must be resolved on the Central Lab Collections forms before shipping can occur. If there are remaining audits for a participant, you will not be able to ship their samples.

Shipping/Storage Boxes

Two sizes of cardboard freezer storage boxes are provided: 2" boxes for serum, plasma, buffy coat and renin specimens in 2 mL vials (10 x 10 grid) and 3" boxes for urine specimens in 8 mL vials (7 x 7 grid). Two boxes of each size are provided: one for returning specimens to the CLCS and the other for long-term storage at BBI. If you do not have access to a -70°C freezer, renin specimens must be shipped to the CLCS within 30 days of collection.

Shipping to CLCS and BBI

1. Forms 30 and 31 contain the detailed participant information for the blood and urine samples. These forms should be filled out while collecting the samples from the participants. After completion, send these forms to the data entry technician for entry in the DASH2 Data Entry system.

2. 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, 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 are for internal use only. They will not be entered. Suggestion: Sort the specimens in freezer into samples going to CLCS and samples going to BBI and by collection date within these two groups.

3. **Create a Box:** Go to the DASH2 Data Management System. Select Central Lab. (See more detailed information on the Central Lab Tracking system in the new insert to your users manual called Central Lab Tracking System User's Manual.) The first step in Central Lab tracking is to create a box for CLCS blood or CLCS urine or BBI blood or BBI urine. You will only be able to work on one box type at a time. The system will search for all your entered Central Lab Collection forms, either bloods or urine depending on the one you choose. It will come back and tell you if you do not have enough samples to fill a box. You can then choose to prepare that box or not. The system will then automatically print out a working draft of the selected shipping log and visual map for you to start packaging the specimens. The visual map is a map of the slots for the particular type of box you will use.

It will fill the slots starting from the bottom left hand corner with the participants who have completed Central Lab Collection forms in the system. The shipping log will have the same information that is on the visual map plus space to write in the shipping condition.

4. **Prepare a box:** Use the working draft of the visual map to fill the slots of the shipping box. The 2" boxes hold 100 x 2 mL vials. They should be packed in the sequence shown on the visual map, starting with the front, left corner of the box, moving to the right, then to the back as each row fills. 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.

   Edit Specimen Shipment Conditions: If any specimens that have been lost, broken, lost labels or become unusable for some other reason, (1) record the condition of the specimen in the shipping condition column, (2) leave that slot in the box empty. If there are any other problems with the specimens (i.e., hemolyzed) and you still plan on shipping that specimen, record the problem with the specimen in the shipping condition column.

5. **Finalize a box:** After all the specimens have been put in the box and the shipping conditions have been recorded. Note: the default shipping condition is “good”, you will only need to note any conditions that are not “good”. Go back into the Data Management system, and select Central Lab/Finalize a Box/Select a box to finalize. You will need to enter the following: Box preparer, prepared date, and any comments. Shipping conditions should have been edited prior to this step. Note: once you finalize a box, you will not be able to modify the data pertaining to that box.

6. **Sending a box:** When all boxes are packed and ready to be sent, you will need to enter the actual sent date in the central lab system. Select Central Lab/Send box/Select a box to send. You will be required to enter the sent date and you can add any additional comments if needed. After entry of the sent date, the system will automatically print out a final shipping log and visual map for you to include with the shipment.

   When the shipping box is packed, make three copies of the shipping log and the visual map. Keep one copy on file at the site, send one copy to the CC, and send one copy with the specimens to the relevant laboratory. Do not send the working drafts.

   Shipping will occur four times during a cohort. The first shipment will be sent to CLCS and BBI following run-in and the rest of the shipments will be sent after each of the three intervention feeding periods. Contact the lab and the repository before shipping. You will need to tell them the shipment date and the UPS/FedEx tracking number.

7. Ship specimens to CLCS and BBI in the large shipping container provided. Obtain sufficient dry ice to fill the cooler. Note: Delay in adding dry ice to the specimens after removal from the freezer will allow specimens to thaw. Insufficient dry ice during shipment will do the

same. Any degree of thawing before analysis will damage the specimens and compromise assay results. Please see the packing/shipping instructions provided by the labs. They will send these instructions with the shipping containers. The CLCS will confirm receipt of shipment with the CC.

8. Notify CLCS and BBI before sending each shipment.
   CLCS: Phone: (314) 362-3522 Fax: (314) 362-4782
   BBI: Fax: (301) 208-8829

9. Specimens must be shipped by Federal Express to:

   Dave Gibson/Core Laboratory
   Washington University School of Medicine
   499 S. Euclid Ave.
   St. Louis, MO 63110
   Phone: (314) 362-3516

   Alfred Chun
   BBI – Biotech Research Laboratories
   217 Perry Parkway
   Gaithersburg, MD 20877
   Fax: (301) 208-8829

10. If you have any specimens left that have not been assigned to a box and shipped, print out the following reports: Central Lab Data Completeness (report #35 in monitoring) and Central Lab Samples to Discard (report #36 in monitoring) to verify the remaining samples. The first report will show the samples we are expecting to send and the second will show those samples of non-randomized participants you will need to discard. If there are any additional remaining specimens that you are unable to deal with using the above reports, please contact Reesa Laws at the CC.

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, place it under the toilet seat, urinate 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 voidings were missed on the tag at the end of the collection.

Women should use the hat to help collect the sample, place it under the toilet seat, urinate into the hat, 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.

<u>You will begin your urine collection at the clinic.</u> 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.

13. OTHER CLINICAL MEASUREMENTS 3

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Weight 3

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Summary of Edits

New changes in Version 1.0

13. Other Clinical Measurements

Height

Height measurements to the nearest 0.1 cm will be taken by certified DASH2 clinical staff at the first (SV1) or second screening visit (SV2). Heights should be measured with the participant standing on a firm, level surface, at a right angle to the vertical board of the height measurement device. The units should be in centimeters. A height board mounted at a 90-degree angle to a calibrated vertical height bar should be used. Check to be sure that the floor is level, that the vertical height bar is mounted at a 90-degree angle to the floor, and that the wall on which the height bar is mounted is straight.

The participant should be instructed to remove shoes and headgear and to stand erect with feet flat on the floor and both heels together, touching the base of the vertical board. The participant is to stand erect with back, shoulder blades, and buttocks in contact against the vertical height board. The participant's weight should be evenly distributed on both feet, and arms should remain relaxed at the sides with palms facing inward. The participant is to stand facing straight ahead with head in the horizontal (Frankfort) plane. The eyes of the examiner should be at the same level as the height indicator bar to obtain the most accurate measurement (Figure 13.1).

Ask the subject to inhale deeply and maintain a fully erect position without altering the load on the heels. The height board should be brought down snugly, but not tightly, on the top of the participant's head. Record the height to the nearest 0.1 centimeter.

Weight

Body weight measurements will be taken to the nearest 0.1 kg by certified DASH2 clinical staff throughout the study. The weight measurement taken at either SV1 or SV2 (at the option of each DASH2 clinical center) will be used with the height measurement to calculate body mass index (BMI, kg/m2) to exclude candidates whose body mass index is in excess of 40.0 Kg/m^2.

Insofar as possible, weight measurements for each participant should be taken at approximately the same time of day in order to minimize variability due to daily eating patterns and activities.

The participant should be instructed to remove shoes, headgear, coat, etc., and heavy items in the pockets (e.g., keys or wallet) in order to be weighed in light indoor clothing. All body weights in DASH2 should be measured on a balance beam or digital scale which is placed on a firm, level surface. If this surface is carpeted, a sheet of wood or hard plastic should be placed beneath the scale.

Ask the participant to stand in the center of the scale platform, since standing off-center may affect the weight measurement. It is suggested that marks be made on the platform to insure the proper position of the participant's feet. The participant should stand with arms relaxed at the sides, head erect, and eyes looking straight ahead.

For a balance beam scale: Be sure the scale is balanced so that the indicator is at zero when no weight is on the scale. Before each weight is measured, the sliding scale weights must be moved to zero. Adjust the weight on the indicator until it is balanced, and record the results to the nearest 0.1 kg. Use extreme care in adding the lower beam weight to the upper beam weight, as they use different increments. Advise the subject to remain standing in position on the scale until the weight has been recorded. This eliminates the possibility of the weight measure being accidentally altered by the balance beam moving as the subject dismounts.

For a digital read-out scale: Make sure the scale reads "0" before the subject stands on the measurement platform. When the digital readout stabilizes, record the observed weight to the nearest 0.1 kg.

Waist (Abdominal) Circumference Measurements

Waist circumference measurements should be taken with an anthropometric measuring tape. Skin should show no marked compression. BE CERTAIN THAT THE TAPE IS KEPT HORIZONTAL WHEN MAKING MEASUREMENTS. To make certain that the tape is kept horizontal, it is best to have an assistant present when taking the measurements or to mount a full length mirror on a wall approximately 1½ to 2 feet from the floor. Since circumference measurements will be made over the participant's undergarments only, a hospital gown may be worn during measurements but the tape should go under the gown. Take one measurement, recording it to the nearest 0.1 cm, then remove the tape from the participant and take a second measurement.

Overview of Procedure

Waist circumference is measured from the horizontal plane at a one centimeter (1 cm) above the navel (measure 1 cm from the top of the navel with a firm ruler and mark this spot in ink). This will usually coincide with the narrowest circumference but has added advantage of being easily reproducible. Be sure that the tape is kept horizontal when making the measurement (either in front of a mirror or with an assistant). Measurement should be made with the participant standing erect, abdomen relaxed, arms at the side, and feet together with weight equally divided over both legs. Tell participants to breathe normally, to breathe out gently at the time of measurement, and not to hold in their abdomen or hold their breath (i.e., at the end of a normal expiration of air).

Equipment Maintenance

Scales used should have been certified at the start of the trial by the local Bureau of Weights and Measures or an equivalent body. Recertification must be completed annually thereafter and posted in the appropriate column of the scale log sheet with any documents provided by the inspector kept on file. This same log sheet is to be used to record bi-monthly in-house checks of scale accuracy. The scale should be tested at two levels to ensure accuracy in the range of weights to be measured during the trial. The lower range will be checked using 20-30 kg weights and the upper range checked using 40-50 kg weights. The technician is weighed on the scale first and this weight recorded. The lower weight is then placed on the scale and this weight recorded. The technician then gets on the scale with the weight and this weight recorded. Then the higher weight is placed on the scale by itself and this weight is recorded. Then technician gets on the scale with the weight and this weight is recorded. These records are requested periodically and checked during site visits. Scales which fail to meet standards within .5 kg at any weight level should not be used for collection of study data and be immediately reconditioned and recertified by the Bureau of Weights and Measures or an equivalent body. All scales used to collect data for the study should be uniquely identifiable either by serial number or a study-specific number printed in indelible ink.

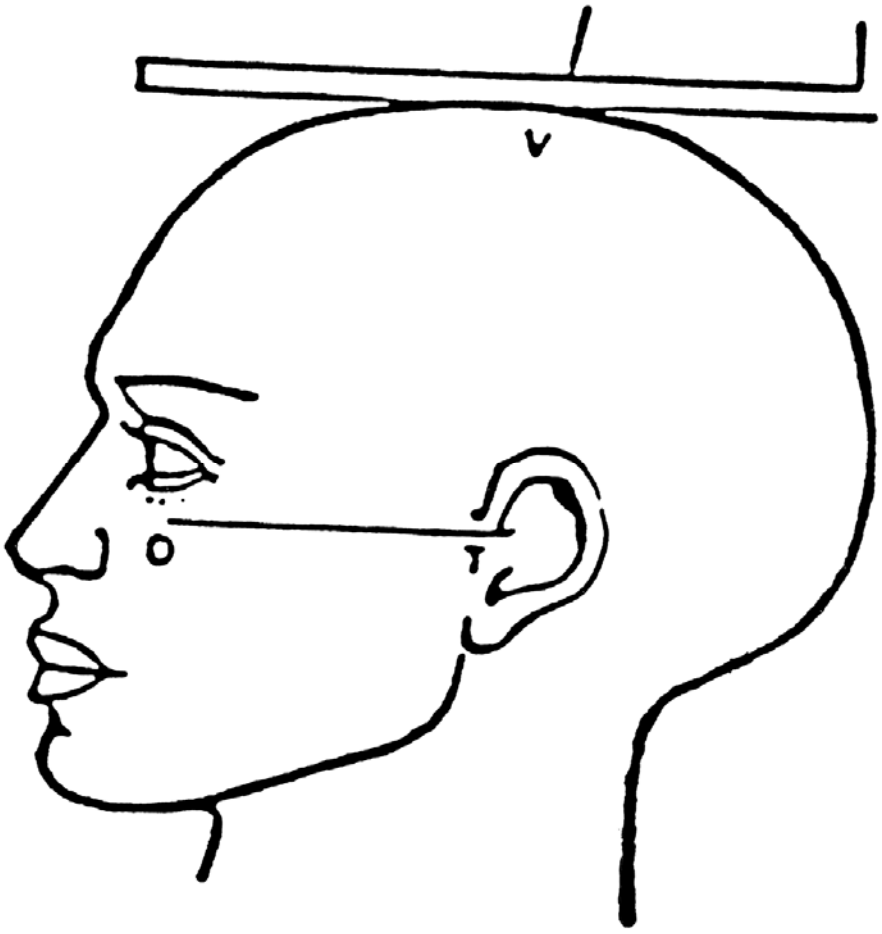
Staff Certification

Certification of a master trainer will be done annually at a central location. At that time the study wide trainer will review the appropriate techniques for measuring and recording height, weight, and waist circumference. All technicians will do duplicate measurements on two individuals. The technician will do the first measurement of both the height and weight on the individual and then repeat the process for the second measurment of height and weight on the same individual. The average of the duplicate measurements on a given individual must be within .2 kg weight and 1 cm height of the master trainer's measurement. In addition, both measurements on a given individual must be within .2 kg/1cm of each other. All technicians trained by the master trainer are authorized to train others. All technicians will also measure waist circumference twice on two individuals. Average waist circumference measurements on a given individual must agree with the master trainer's measurement within 2 cm, and both readings on a given individual must agree with each other within 2 cm. Individuals at the sites may be trained as appropriate by the trainers. The following forms will be completed by the trainer on each person trained and copies sent to the coordinating center:

1. Weight Certification Form (#64)
2. Weight Observation Checklist Form (#63)
3. Height Certification Form (#67)
4. Height Observation Checklist Form (#66)
5. Waist Circumference Certification Form (#69)
6. Waist Circumerence Observation Checklist Form (#68)

Figure 1

Frankfort Plane for measuring body height



ORBITALE: Lower margin of eye socket.

TRAGION: Notch above tragus of ear or at upper margin of zygomatic bone at that point.

FRANKFORT PLANE: Orbitale tragion line horizontal.

14. DATA MANAGEMENT 3

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Summary Edits

14. Data Management

Staff ID's

All DASH2 staff must have a DASH2 staff ID number. To obtain a staff ID number, the clinic coordinator should e-mail the Data Manager at the Coordinating Center with the following information:

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

The Coordinating Center will assign a new number within 24 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:

Patient identification and record linkages. The ID in each form needs to be checked for transposition errors. The format must be "aaaaa#####." The initial 3 alpha characters must be the same as the first three letters of the participant's last name. The next 2 alpha characters must be the same as the first two letters of the participant's first name. The last five digits are a unique identifying number for that participant. Each page of multi-page forms must have the same ID number. ID labels can be generated after each screening visit, before run-in and before each intervention period to help assure accuracy.

Legibility. All data must be checked for illegible handwritten replies, spelling errors, etc. All checked response boxes must have checks within designated spaces. Check to be sure that the forms are filled out in pen. Forms filled out in pencil are often difficult to read.

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

Missing information. All forms must be checked for unanswered items or sections of an otherwise completed form. The clinic coordinator must assure that all necessary forms have been completed for the indicated visit or activity before entry of the individuals visit data can begin. Only four DASH2 forms may have missing data: participation survey, post-anonymous

survey, diet acceptability and patient history. All other DASH2 data collection forms must be complete prior to data entry.

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

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

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

Data Edits on Forms

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

- Participant responses should never be obliterated.
- A 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 8/5/98 Addition error

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

- verify that the response is clearly written.
- 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 8/5/98 participant correction

Data Entry

All forms will be batch entered by a DASH2 certified data entry technician. Range and logic checks are built into the system to try to deal with form discrepancies before entry. The data entry technician should enter the data as is from the form. The values not meeting the defined range and logic check criteria will be put into an audit history table for the clinic coordinator to resolve. The goal for data entry is to be current within two weeks in order for reports to be accurate and to minimize the number of corrections that will need to be made at one time. The one exception is the Daily Diary; this form should be entered on a daily basis.

Data Entry Flow

All data collection forms for a visit should be entered before the corresponding visit/flow forms. All forms including the visit/flow forms should be entered before the closeout forms.

For example: You just finished run-in for a participant….

1	Enter all daily diaries not previously entered
2	Enter all data collection forms:
	Patient History
	BP 1 and BP 2
	Symptoms form
	Medication questionnaire
	Diet Acceptability questionnaire
	Case Conference form
3	Enter the Run-In flow form
4	Enter Close out form if relevant

Quality Control Methods Following Data Entry

As the data entry technician enters the data, any values that do not pass the range or logic checks defined by the system will trigger a prompt to the data entry technician to confirm that it was correctly entered. If it is not a data entry error and the technician confirms that it is entered as coded, an audit record will be written to an audit history table. This table will contain the participant ID number, visit, visit date, the dataset, the value in question, error type and place holders for the corrected value, correction date and staff ID to be entered. The data entry system will not allow any additional entry of data for a participant until the audit is resolved. The clinic coordinator will need to keep up with these on a weekly basis to assure accuracy of reports and timeliness of data entry. If there are any questions, Reesa Laws should be contacted at the CC.

Data Edits to Database

Most corrections can be made at the sites with the audit history table in data management or with the data edit feature in the DASH2 Data Entry System. See the Data Entry User's Manual and

the Data Management User's Manual's for details on these processes. Certain types of corrections will need to be made by the Coordinating Center due to potential conflicts in the data fields (e.g. a participant was closed out in error).

To have a correction made by the Coordinating Center, send an e-mail to the Data Manager at the Coordinating Center with the participant ID, the name of the form, the date on the form, the data field in error and an explanation of the correction. The Coordinating Center will make the change and send an e-mail confirmation that the change has occurred. The clinic coordinator should also make these changes on the relevant participant data form (see "Data Edits of Forms" section above).

Centrally-entered data

Centrally-entered data will need to be sent to the Coordinating Center for entry. The only DASH2 form that is entered at the Coordinating Center is the Food Frequency Questionnaire (FFQ). Before sending to the Coordinating Center, sites should make copies of the FFQ for onsite archiving for the length of the study. The original FFQ form should be sent to the Coordinating Center. A shipping log (form #36) specifying ID's of forms sent should accompany each mailing. A copy of this shipping log should be archived at the mailing site for reference and confirmation of form receipt. When receiving bundled mailings, the Coordinating Center staff will review the shipping log and assure that all reported forms were received. This should be noted on the shipping log, which will then be archived at the coordinating center. Any discrepancies will be immediately reported to the site, who will help resolve the problem. Resolution may include making additional copies of the archived data and re-mailing them to the Coordinating Center. The FFQ's should be mailed to the Coordinating Center after run-in is complete. Only FFQ's of participants who were randomized should be sent to the Coordinating Center.

Data Validation

The primary measures of data integrity rely on the verification of data. Verification is a comparison of data before a transition (data entry) to the result after the transition to assure a one-to-one correspondence and assure that the transition process was "true". In order to assure the accuracy of the DASH2 data, the Coordinating Center has set up a two step process. 1) Validation of the data by the Coordinating Center completed at the end of each cohort and as a part of a site visit. 2) Validation completed by the individual sites.

Data Validation at the CC

Data validation will be done by the Coordinating Center to assure validity of the data. The Coordinating Center will request the following at the end of each cohort:

- All Blood Pressure forms for randomized participants

- Three charts chosen at random from randomized participants. This includes all clinical and diet forms entered into the DASH2 data entry system.

Additional validation will occur as a part of site visits. The Coordinating Center will request a random set of forms (from both randomized and non-randomized participants), as well as three random charts from each site.

The site should copy the requested forms and complete the accompanying shipping log (form #36) and send to Reesa Laws at the Coordinating Center. 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 Coordinating Center. Changes that need to be made to the database should be clearly noted on the form. The Coordinating Center will file all copies of the forms in the Coordinating Center's participant chart.

Data Validation by the Site

The Data Management system has several data validation reports available for the sites to validate their own forms. There are reports to view all screening data, 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 DASH2 Data Entry User's Manual for details.)

Archiving

A copy of each site's master database will be transferred nightly via phone lines from the site's file server to the coordinating center's file server. Archiving will occur automatically at the coordinating center, which will contain the previous day's data from the sites on-line and all historical data off-line. The historical data is easily obtained if restoration is needed. In addition, all data collection forms need to be archived for the life of the study in hard-copy form so that copies may be sent to the coordinating center as needed for data management. Requests for copies of archived data will be made on a form-by-form basis by the Coordinating Center.

Use of DASH2 Computing Equipment

Kaiser Permanente Center for Health Research (CHR), as DASH2 Coordinating Center, is supplying the following equipment for use by DASH2 Study intervention sites:

- 1 DELL P200/GsM Desktop Server system
- 1 Lexmark Optra R+ printer
- All Required peripherals, batteries, cables, and connectors

CHR retains rights of ownership for this equipment and all installed software. The equipment and software are provided for the sole purpose of conducting DASH2 activities as specified in the DASH2 Manual of Procedures (MOP). These activities include, but are not limited to, study communications, data entry, data transfer, reporting, data edits, and data repairs. This equipment will be returned to the CHR upon demand.

Additional uses or modifications of the equipment, software, and/or configuration, are not authorized, except as approved by the Coordinating Center Data Manager, and are considered a violation of study procedures. Non-authorized use or modification include but are not limited to: personal use of equipment or software, making and/or distributing unlicensed copies of DASH2 study software, installing additional software, making configuration changes to equipment or existing software, or connection to non-study networks.

Any request for exceptions to this policy must be authorized by the DASH2 Coordinating Center Data Manager prior to action.

Other DASH2 Technical Manuals

Please refer to the following manuals for technical details/instruction:

- DASH2 Console User's Manual
- DASH2 Data Entry User's Manual
- DASH2 Data Management User's Manual
- DASH2 Lab Tracking User's Manual

16. TRIAL MONITORING REPORTS 3

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Summary of Edits

16. Trial Monitoring Reports

Introduction

During the trial's course, the 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.

Current versions of the standardized reports can also be generated on demand using the file servers. This allows individual sites to get up-to-the-minute reports as often as they wish, further enhancing data quality.

Types of Reports

Recruitment/Follow-up Reports

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

Baseline Data Reports

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

Quality Control Reports

Quality control reports include a number of reports related to the integrity of the DASH2 database and adherence to trial protocol by both participants and sites. These include audit reports, digit preference reports, and blood pressure protocol reports.

Laboratory QC and Results Reports

Laboratory quality control reports summarize lab tracking, including receipt, receipt status, and the collection of process measures such as start and stop times for 24-hour urine samples that will be used to establish the usability of data laboratory results reports summarize results of laboratory analyses.

Side Effects Report

The side effects report summarizes side effects reported by DASH2 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 1-2 weeks prior to the meeting or conference call of each committee. Not every report is sent out in every mailing. The Coordinating Center reviews the available reports before each mailing and sends only those reports that have new and/or relevant data.

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

Monthly Recruitment Committee Reports

These are distributed by the committee chair a week prior to the meeting or conference call.

- 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

Reports Available on Site File Servers

- These reports are available at all times and are always current within the last 48 hours.
- Baseline Data Reports
- Quality Control Reports
- Laboratory QC and Results Reports
- Side Effects Report

17. TRIAL COMMUNICATIONS 3

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17. Trial Communications

Importance of Trialwide Communications

Maintaining lines of good communication is one of the keys to the successful operation of a long-term collaborative clinical trial. During the course of the DASH2 study the coordinating center will be responsible for the following tasks that depend heavily on effective communication channels and skills:

1. arranging orientation and initial training of clinical center personnel,
2. monitoring project adherence,
3. reporting to Project Office and committees and DSMB,
4. responding to clinical center and Project Office requests,
5. staffing trial committees, including logistic arrangements and distribution of meeting minutes.

The tools of communications for DASH2 include: regular meetings of the Steering Committee and its subcommittees, conference calls, sequential memos, telephone calls, data edit reports, and routine trial monitoring reports.

This section summarizes the principles for DASH2 communications and describes the procedures for sending communications between participating institutions.

Principles of DASH2 Communications

Central Contact Person at Each Location

A key component of the DASH2 communications protocol is that each participating institution identify a single person who serves as the contact person for that site. All DASH2 communications directed to a site should be sent to that person, who is then responsible for forwarding copies of the document as appropriate. In the event that this individual is not available, backup coverage is arranged so that someone else checks for incoming correspondence on a daily basis.

This procedure assures, for example, that an urgent fax is not left unread for several days because the individual to whom it was sent is out of town. Instead, the contact person would review the message and forward it to someone else who can respond in a timely manner.

Rapid Turnaround of Minutes

Especially during the initial planning stages of a trial, the work of the trial is done by committees who meet to design the trial and work out the various procedures. In order that this process proceed smoothly, it is critical that accurate minutes of committee meetings be taken and then distributed in a timely manner. The coordinating center takes notes during all DASH2 committee meetings and will attempt to send out within two weeks of their occurrence.

Rapid Turnaround of Queries

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

Elements of Communications Network [Bryce and Reesa will define the following sections after new equipment is in place at the sites]

During the initial, planning phase of the trial the coordinating center has relied mainly on a combination of FAX, Email, regular mail, and UPS to send written study communications and materials.

As of July, 1997, each of the clinical centers will have in place an operational PC file server as part of the DASH2 data management system. In addition to using the file server to transmit study data to the coordinating center, the file server can also be used to send electronic mail and formatted study documents.

DASH2 forms, most reports, the Protocol, and the current version of the MOP will be posted on the file servers. The coordinating center also will use the files servers to send the majority of DASH2 documents, including meeting minutes and memos to the clinical centers largely bypassing the need for FAX, Email, regular mail, and UPS communications.. These mechanisms will still be used, however, for communications with the Project Office and other sites who do not have file servers.

Sending and Receiving Mail/Documents on the File Server

Introduction

The CC will make daily electronic connections with site file servers via "PC Anywhere." The purpose of these connections will be four-fold: 1) to transfer study data from the sites to the CC; 2) to update forms as needed; 3) to repair data as needed; and, 4) to swap electronic mail (Email). This section describes the procedures for the fourth purpose, Email.

Directory Structure

Email activity at the sites will occur in one of two subdirectories. These subdirectories are **C:\DASH2\Receive** and **C:\DASH2\Transfer**. C:\DASH2\Receive will be used by the CC for placing documents and files that come from the CC for use by the site. C:\DASH2\Transfer will be used by the sites for placing documents and files that they want picked up by the CC for CC use or transfer to another site. Simply, C:\DASH2\Receive will be the site incoming mail box and C:\DASH2\Transfer will be the site outgoing mail box.

Schedule

Pickup and delivery will generally occur once a day. Unreachable systems may cause pickup and delivery to occur less frequently. Special Pickups and Deliveries may be arranged on an individual basis by calling the CC, who will process these special request as time allows.

Housekeeping

The C:\DASH2\Receive and C:\DASH2\Transfer subdirectories should be used by sites as staging areas, rather than archives for historical files and documents. Just as you wouldn't use your mailbox at home for long-term storage or filing of your mail, neither should you use these directories for this purpose. Files that are received in C:\DASH2\Receive should be moved to an appropriate subdirectory immediately. The selection and/or creation of the appropriate subdirectory, other than C:\DASH2\Receive or C:\DASH2\Transfer, is left to the discretion of the sites. The CC will delete files from C:\DASH2\Transfer as they are transferred from the site to the CC.

IMPORTANT - This means that if the sites wish to maintain copies of these transferred files they will need to maintain their copies in another subdirectory. In addition to good housekeeping principles, the other reason for this process is that if the CC sees files in the receive directory the day after sending the files to a site, they can assume that the receipt of the files has not been acknowledged. This is important if the files need timely attention. Along the same lines, if a site sees files in the C:\DASH2\Transfer subdirectory the day after placing the files there, they will know that the CC has failed to grab these files. This, too, is important if the files need timely attention.

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Summary of Edits

New changes in version 1.1

- Change in amount of time allowed for repeat BP after an escape level 1 for both run-in and intervention.

18. Safety Monitoring

Blood Pressure

In order to prevent a prolonged period of untreated hypertension (outside the eligibility range of DASH2), 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 three 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 potentially dangerous blood pressure elevation. Participants may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment even though the BP is below the escape thresholds.
- 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. The original is placed in the participant's chart at the site, and a copy is sent to the CC.

DASH2 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 qualified 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 section 6 of the DASH2 Protocol. At each screening visit, the exclusion limits are based on all blood pressures averaged up to that point. In the event that the mean SBP 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 RZ blood pressure measurement must be obtained within four days and still during run-in. 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 RZ blood pressure measurement must be obtained within seven days and still during run-in. 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 who are 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 RZ 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 RZ 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, qualified, blinded personnel at the clinical center who are not affiliated with DASH2 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 DASH2. If clinical problems arise from DASH2 participation, the problem may be dealt with at the clinical center or through referral as is most appropriate and consistent with the institution's risk management procedures.

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 12 of the Protocol and she is excluded from further participation in the study.

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. For detailed information on procedures to ensure food safety, see DASH2 Diet MOP, Chapter 11.

Other Adverse Events

Throughout the run-in and intervention feeding periods, the Daily Diary (Form #24) is used to capture information about possible symptoms from the study foods. Particular attention is paid to symptoms of lactose intolerance and to other gastrointestinal symptoms. Participants also complete a more comprehensive symptoms questionnaire (Form #11) at the conclusion of each feeding period.

Severe or potentially clinically significant symptoms are brought to the attention of a DASH2 clinician, and feeding is terminated if symptoms or signs related to a DASH2 diet are deemed by the participant or DASH2 clinician to be intolerable or dangerous. To the extent possible, staff

collect end-of-intervention measurements on such participants, giving first priority to the five end-of-intervention blood pressure measurements.

The clinical centers are expected to formally document the occurrence of any unusual or significant health problems that arise during feeding and require medical intervention. Participants are asked about such events at the end of each feeding period as part of the Symptoms Form (#11), and their occurrence is documented on the Serious Adverse Events Form (#12) which is sent to the Coordinating Center.

Interim Stopping Guidelines

In addition to the above rules for monitoring the safety of individual participants, the external Data and Safety Monitoring Board (DSMB) regularly reviews the trial's progress, including unblinded interim results, and recommends 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.

Comorbid Conditions

Selected comorbid conditions, such as insulin-dependent diabetes and renal disease, lead to exclusion from DASH2. These are discussed in detail in Clinic MOP Chapter 4.

Laboratory Abnormalities

Participants are informed of any clinically significant laboratory abnormalities based on local laboratory analyses done as part of screening, whether or not these constitute an exclusion to DASH2. These laboratory data are supplied to the participant and to his physician for follow-up.

19. PARTICIPANT CLOSE-OUT 3

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Summary of Edits

Changes in version 1.1

- Took out references to close out activities that are located in the Diet MOP, chapter 37.
- Clarified close out instructions for the data entry/data management system for each timepoint (i.e., during screening, between visits, during run-in, after randomization)
- Added section for end of cohort close out instructions

19. Participant Close-out

Purpose

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

Close out Prior to Randomization

If a participant refuses to participate in the study or becomes ineligible prior to randomization, they need to be closed out of the DASH2 data entry system in one of two ways.

At a screening visit: If refusal/ineligibility is determined at a screening visit, the participant can simply be closed out by marking "ineligible" or "refusal" on the bottom of the relevant screening visit form and then entering that form into the system. The form should also specify the reason for ineligibility. *All data collection forms for that participant for that visit should be entered into the DASH2 data entry system before closing them out with the visit form.*

Between screening visits: If refusal/ineligibility is determined between screening visits, the participant can be closed out using the Close out form (#18). For example, a participant's local lab results may be received in between SV2 and SV3 or a participant may call in to cancel their next screening visit and refuse to participate any further. *All prior screening data collection forms should be entered before closing out the participant.*

During run-in: If refusal/ineligibility is determined during run-in prior to randomization, the run-in flow form (#16) needs to be filled out and entered with an outcome of "ineligible" or "refusal". In addition, the Close out form (#18) should be completed and entered. Be sure to review the coding instructions on the Close out form for additional close out codes. If the close out reason is coded as "other", the clinic coordinator should fax a copy of the close out form to the CC data manager for review. The CC will add additional codes if necessary or recode the "other" response if possible. *All data collection forms for run-in should be entered before entering the run-in flow form and the close out forms.*

Early Termination after Randomization

Participants who suffer a morbid event with a lasting effect on blood pressure (e.g., myocardial infarction, stroke), who start on blood pressure medications, or who die during the study are considered terminated as of the date of the morbid/mortal event or start of medications. Where possible, these individuals and any other participants who are unable to complete the study for any reason should receive a close-out briefing similar to that described in chapter 37 of the DIET MOP. This briefing should occur as soon after the terminating event as the participant's condition permits. However, it need not be done as a face-to-face meeting; the information may be sent by mail.

The run-in flow form (#16) or the Intervention flow for (#20), whichever is relevant, should be completed with a outcome of "drop out". In addition, the Premature Study Termination Form (#22) and Serious Adverse Events Form (#12), if relevant, should be completed on the participant and entered into the DASH2 data entry system. Be sure to review the coding instructions on the Premature Termination Form for additional termination codes. If the termination reason is coded as "other", the clinic coordinator should fax a copy of the termination form to the CC data manager for review. The CC will add additional codes if necessary or recode the "other" response if possible. The second section of the Premature Termination form asks if the participant was unblinded after randomization. If the participant came in for any intervention meals, they are considered unblinded and coded as such. See Unblinding section for more details.

Note also that for anyone who drops out of the study prematurely, for whatever reason, DASH2 personnel should try to obtain a complete set of end-of-diet period (i.e., participation survey, medication questionnaire, BP measurements. See the intervention chapter for a complete list.). If this is not possible, first priority should be given to collecting as many of the five end-of-feeding period RZ blood pressure measurements as possible.

Unblinding

DASH2 participants are kept blinded to their intervention group status and their mean blood pressure measurements for each feeding period until the conclusion of the full trial. The reasons that participants remain blinded until the conclusion of the trial are as follows. Once data collection on any given participant is complete, the unblinding of treatment assignment and blood pressure results cannot affect that person's data. However, the staff person presenting the data would also become unblinded to that person's results, and over time could develop subjective opinions about the efficacy of the various interventions. This in turn could influence the manner in which this individual interacts with other study participants. Also, participants may be recruited from the same pool and may know one another. Thus, a participant who is unblinded to his treatment assignment may develop subjective opinions about the efficacy of the interventions and could influence other study participants who are currently enrolled in the trial or who may enroll in the future.

End of Cohort Close Out

This section contains instructions on the final closing out of participants from the DASH2 data management system. Refer to Chapter 37 in the DIET MOP for detailed instructions on close out activities with the participants.

All participants should have all data collection forms entered into the DASH2 data entry system. After entry is complete, the intervention flow form (#20) for IFP/III should be completed and entered. Entering the last intervention flow form effectively closes out all randomized participants. The intervention completeness report located in the data management system should be run to verify that all participants have been closed out.

The Participants in Limbo report located in the data management system can be run at any time to identify any non-randomized participants that still have an “eligible” code in the system and need to be closed out. The data needs to be resolved for all participants on the Participants in Limbo report by the end of the cohort.

20. AMBULATORY BLOOD PRESSURE MONITORING 3

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Summary of Edits

Changes in version 1.1

- Clarifications made to down-loading the monitor section
- Set up section added to preparing scans for exporting
- Clarifications made to preparing scans for exporting section

Changes in version 1.2

- Clarifications made to uploading the data to file server section
- Added reference to the certification (data) system to the training and certification section.
- Added section for ABPM placement certification only

Changes in version 1.4

- Added item to Comparison of ABP Monitor to Conventional Device list
- Added inspection section under the Maintenance of ABP

20. Ambulatory Blood Pressure Monitoring

Introduction

Twenty-four-hour Ambulatory Blood Pressure Monitoring (ABPM) will be performed at the end of each intervention feeding period. This procedure should be performed during the same time period when we are measuring RZ blood pressures, i.e., the last 9 days of each intervention period.

Equipment

ABPM software data key

Install ABP software on an IBM PC or compatible computer. The data key is attached to the computer parallel printer port. Attach the printer cable to the data key. Printer operation will not be affected.

ABP monitor

The SpaceLabs Medical Model 90207 Ambulatory Blood Pressure (ABP) Monitor is a small, lightweight battery-powered unit designed to take blood pressure and heart rate measurements. The monitor has the following features:

- 4-digit LCD display
- Battery powered
- serial communications port
- power on/off switch
- blood pressure cuff

Monitor Cable

The monitor cable is attached to a serial port on PC either on the port above the data key or along side the data key. The other end of the cable attaches to the monitor arrow to arrow.

Cuffs

Tru-Cuff are reusable, single hose, and can be self applied.
Cuff sizes are as follows:

- adult 17-26 cm
- adult 24-32 cm
- large adult 32-42 cm
- XL adult 38-50 cm

The cuff hose can be positioned for either the left or right arm. To apply the cuff the hose should lead from the appropriate opening on the cuff. [A drawing of a person with a break in its arm indicates the arm the hose is positioned.] To change the position of the cuff, remove the bladder by pulling it through the hose opening. Turn the bladder in the opposite direction. Using fingers only, fold or roll up the bladder to fit in the opening. Do not use pencils, pens, or other hard objects as damage to the bladder may occur. Spread the bladder flat inside the cuff. Cuff wraps with bladder removed can be machine washed on delicate cycle or soaked in mild detergent.

Advance Notification of the Participant

Inform the participants one or two days in advance that 24-hour ABPM will be measured and that this visit will take 10-15 minutes longer than a normal blood pressure check. Ask the participant to wear a short-sleeved shirt or blouse, or a garment with loose sleeves, to accommodate placement of the cuff.

Programming/"Initializing" the ABP Monitor

The DASH2 procedure for programming the monitor to take automatic blood pressure readings is as follows:

1. Insert fresh batteries into the monitor (if new batteries were not inserted at the end of last session).
2. Log in to your computer and bring up windows. Double click on the ABP Report Management System icon.
3. Turn on monitor.
4. Be sure the ABPM cable is attached to the appropriate port on the computer and to the monitor (arrow toward arrow).
5. From the menu bar click on " Communications." From the "Communications," choose "Init monitor."
6. To set the default settings choose "Setup" from the menu bar. Choose "monitor' from the pull down menu. From the settings menu choose "New" to change the settings as to DASH2 protocol (See Table 1). To accept default settings click on save, then OK
7. If you know who will be wearing the monitor, enter the subject's full DASH2 ID in the "Patient Name" field followed by "a" if this is the first feeding period, "b" is this is the second feeding period and "c" if this is the third feeding period. Add a "1" or "2" after the a, b, or c, indicating whether this reading was the first attempt (1) or a repeat of an unsuccessful attempt (2), (for example, if the full DASH2 identifier is SVELA12345, enter SVELA12345a). ~~,~~ In ~~In~~ the "Patient ID Number" field, enter the five numbers of the DASH2 identifier followed by "a" if this is the first intervention period, "b" if the is the second intervention period, or "c" if this is the third intervention period. Add a "1" or "2" after the a, b, or c indicating the first attempt (1) or a repeat of an unsuccessful attempt (2) (for example, if the full DASH2 identifier is SVELA12345, enter 12345a2). If you are initializing the monitor for future use (i.e., don't know the name of the subjects), enter 9999 both in

the "name" field and in the "ID number" field. You must then enter the correct DASH2 ID and number when you download later.

8. Click on "Start Inil" to initialize the monitor. Disconnect monitor from cable, turn it off, and place monitor in its padded carrying case.
9. Fill out the top section of the DASH2 ABPM Initialization/Downloading Checklist (Form #59). The day before placing ABPMs on participants, put a patient ID label on each monitor and a patient name label on the padded carrying case. This will ensure that the correct ID is used when data are downloaded.

TABLE 1

Monitor Initialization Default Settings
Initialization Name: DASH2

☐ Show results of readings
☐ Clinical Verifications Setup
☐ Display Cuff Pressure
Show clock time in: 0 12 hour 0– 24 hour

Period	Starting Hour	Ending Hour	Cycle Time	Tone (Y/N)
1	0	6	30	N
2	6	0	30	Y

Placement of the BP Monitor on the Participant

The DASH2 clinician will take two RZ readings as per the usual DASH2 protocol and record these on the usual BP data form and also on the DASH2 ABPM Placement Form (Form #27). While the subject is still seated, place the ABPM blood pressure cuff on the participant's non-dominant arm (e.g., on the left arm if the subject is right handed). ***Use the SpaceLabs cuff size in the range of the Run-In ~~SV1~~ arm circumference measurement*** *Record which arm you used on the ABPM Placement Form (Form #27). Be sure that the cuff is set-up to be used on the arm where you are placing it. If not, reverse the orientation of the bladder inside the cuff before placing it. Position the cuff with the arrow directly overlying the brachial artery. Place an "X" with a marker over the participant's brachial artery so they know where the arrow should point. Keep the lower edge of the cuff (toward the elbow) at least one inch above the antecubital fossa. Pull the self-tightening cuff so that it is snug but not uncomfortable. As you are doing this, show the patient how to orient the arrow on the cuff and how to loosen and tighten the cuff. If cuff covers antecubital fossa, do not conduct ABPM on this participant.

[*For subjects who require a thigh-sized cuff during RZ measurements, try the XL cuff for ABPM. This goes up to a 50-cm arm circumference. If the arm circumference is larger than 50 cm, then do not conduct ABPM in this participant.]

Next, allow the subject to remove the cuff altogether and replace it. Once it has been correctly replaced, connect the tubing of the cuff to the ABP monitor itself. Turn the monitor on and initiate a BP reading by pressing the blue button on the top of the monitor and hold the button down for 5 seconds. The monitor display will show a numerical countdown sequence and begin to inflate. After the monitor has deflated and the reading is completed, check the systolic, diastolic, and pulse rate values on the monitor display. Record these values on DASH2 ABPM Placement Form (Form # 27).

IMPORTANT: Record the time that the ABP monitoring was initiated. (Note: noon = 12:00pm) Wait 30 seconds and take another blood pressure by pressing the blue start button and record these values as well. If these two blood pressure readings do not indicate an "error" signal on the display, the unit has been successfully placed. Manually abort the next three readings by pressing the blue button once to start and once to stop (do this three times). This is done to prevent the participant from seeing their BP (the monitor displays BP for the first five readings only). If the subject refuses to wear the ABPM, this must be noted on the DASH2 ABPM placement form and placed in patient's file.

Give the subject the Instructions to Participants (Form #60). Review these instructions verbally. The subject is then ready to leave the clinic. Complete the remaining fields on the DASH2 ABPM Placement Form (Form # 27).

Reading/ "Down-Loading" the Monitor

When the subject returns to the clinic the day after the monitor has been placed, the monitor can be removed if it has been worn for a full 24 hours (check ABPM Placement Form (Form # 27) for time placed). If not, ask the subject to wait a short time until a 24-hour recording has been obtained (if possible). You may then remove the cuff from the subject's arm and take the cuff and monitor to the ABPM computer. Ask the participant to complete the DASH2 ABPM Participant Questionnaire (Form #28). Enter the participant's DASH2 ID number on the top of the Form.

To Read the Monitor:

1. Access the ABP Report Management Systems in windows. Connect the monitor via the cable (arrow to arrow), turn monitor on, click on the "Communications" and choose "Read Monitor" from the pull down menu. The system will ask for a unique 9-digit number. Enter the 5 digits of the subjects DASH2 ID followed by 4 zero's. When "Select A Group" message box appears, select DASH2 from the scan groups. Click OK
2. The screen will display the subject's DASH2 ID and identification number (this may be 9999 if that's how the monitor was initialized).
3. If initialized with 9999, change the name field to the DASH2 ID --followed by "a" if this is the first feeding~~feeding~~ period "b" if this is the second feeding~~feeding~~ period and "c" if this is the third

feeding~~feeding~~ period. Add a "1" or "2" after the a, b, or c, indicating whether this reading was the first attempt (1) or a repeat of an unsuccessful attempt (2). *Example: The File Name assigned to subject # SVELA12345 for his end-of-intervention period 1 ABPM recording would be SVELA12345A1*. To save changes, click "File" and choose "Save" from the pull down menu.

4. To review data for BP adequate readings click on "Review" from the menu bar and choose "Raw Data Tables" from the pull down menu. Count to be sure there are at least 14 acceptable readings between 6:00 AM and 12:00 midnight. If so, the monitor is acceptable. If fewer then 14 readings, the subject should be asked to repeat the monitor. To save data choose "File" from the menu bar and "Save" from the pull down menu.
5. Complete the center section of the DASH2 ABPM Initialize /Downloading Checklist (Form 59).
6. To initialize the monitor for the next subject, repeat steps in "Programming / Initializing" the ABP Monitor.

Preparing Scans for Exporting

From the main menu choose "setup" then "group" from the pull down menu. The setup Scan Group Screen Appears. Under scan groups on the left should be 3 entries: default, DASH2, and ABP (Drive A). Highlight the ABP (Drive A). Change the group settings as follows:
Name: ABP (Drive A)
Import Directory A:\
Export Directory A:\
Work Directory A:\
Click on save
Choose the DASH2 directory from "setup" then "Group." Change the setup as follows:
Name: DASH2
Import Directory: C:\DASH2\Import
Export Directory: A:\
Work Directory: C:\DASH2\work
Click on save

1. Click on "File" and choose "EXPORT" from the pull down menu. The scans in your DASH2 group should be displayed. If not, change the Scan group to DASH2 from the pull down arrow under the scan screen.
2. Select the scan(s) to EXPORT by highlighting each scan or by selecting "Mark all".
3. Insert your floppy disk on to the "A" drive of your PC.
4. The "Export ABP Scan" box will appear. Choose FT format for the export format. "File Name" will appear in the menu bar (this should be the DASH2 identifier code plus "A, B or C" and a 1 or 2). Click on OK. You must repeat this step for each scan you export.
5. The ABP file will now be on your floppy disk ready for uploading to the file server.

~~*To be sure each site ABP Monitor system is working properly, the trainer at each site should go through the entire procedure for intializing, reading, copying to a floppy disk and transfer to the file server before the beginning of cohort 1. Check with the CC as to were they want the test ABPM reports transferr*~~

Procedure for uploading ABPM data to the DASH2 file server

1. Check the contents of the floppy disk. You can do this by putting the floppy in the disk drive of any computer (except the file server) and then using My Computer or Explorer to view the contents of the floppy. If you have exported the ABPM data correctly to the floppy, you should see a list of files that looks like:

   10001a1.d00
   10001a1.f00
   10001a1.p00
   10002a1.d00
   10002a1.f00
   10002a1.p00
   ...

   If your list does not look like this, do not load the data onto the file server. To fix the problem:
   - Make sure the floppy is blank before you start the process of exporting the ABPM data.
   - Make sure you are using the latest instructions on how to export the data.
   - Try the export again following the instructions carefully.
2. Take floppy disk to file server and insert it into the file server floppy drive.
3. Select File, Get From, ABPM after logging onto the DASH2 file server.
4. The ABPM files will be copied to the ABPM subdirectory under the SITEWORK directory. The new ABPM files will be transferred overnight.
5. Remove floppy disk from the file server floppy drive.

Complete the bottom section of the DASH2 ABPM Initialize/ Downloading Checklist (form # 59)

To be sure each site ABP Monitor system is working properly, the trainer at each site should go through the entire procedure for initializing, reading, copying to a floppy disk and transfer to the file server before the beginning of cohort 1.

Maintenance of ABP Monitor

Overview

Each clinical center is responsible for the proper operation and maintenance of its ABP equipment. The clinical coordinator assumes responsibility for proper maintenance and all staff are instructed to report promptly any real or suspected equipment problems to that person. All checks and inspections are documented and recorded by date in a permanent log maintained separately~~separatly~~ for each unit. Problems and solutions are also recorded. All maintenance logs (form #88) should be stored in a permanent binder.

Comparison of ABP Monitor to Conventional Device

To check the calibration of the monitor use the following procedure.

1. Obtain a full size mercury sphygmomanometer.
2. Disconnect the cuff hose from the monitor.
3. Connect the cuff T-tube to the monitor Luer-Loc connector and the sphygmomanometer.
4. Insert a rigid cylinder in the cuff and fasten the cuff as you would on a person's arm.
5. Press the Start/Stop button on the monitor. The display should read approximately 165. Compare the readings on the monitor and the sphygmomanometer as the pressure bleeds down. The monitor readings should be within three millimeters of the sphygmomanometer readings or 2% of the reading, whichever is greater. At the end of the procedure, the monitor displays an event code.
6. Disconnect the T-Tube from the monitor. Disconnect the air hose and the sphygmomanometer from the T-Tube. Reconnect the cuff to the monitor.
7. The annual comparisons should be recorded on the ABP Monitor Inspection and Maintenance Log form (#88).
8. If a monitor has more than a three millimeter or 2% difference in the comparison, the monitor should be returned to Space Labs for calibration.

Periodic Maintenance

Periodic maintenance consists of replacement of the batteries used in the monitor, the main battery and the backup battery. The AA alkaline batteries are the main battery and must be replaced before each use. The Lithium battery is the backup battery and should be replaced as needed. The computer will prompt you when the lithium battery is getting low. Check the Space Labs Operation Manual for proper placement of batteries. Centers should keep extra lithium batteries on hand.

Inspection

All monitors should have a visual inspection before each cohort. This should include all working parts especially the AA battery connectors. Check the cuffs for tears in the sleeve and breaks in the tubing. Any problem cuffs should be replaced with a new cuff. Problem monitors should be sent to Space Labs for repair. Record inspection results on form #88.

~~***Procedure for uploading ABPM data to the DASH2 file server***~~

~~1. Copy individual ABPM files from the PC your site is using for ABPM processing to a floppy disk.~~

~~2. Take floppy disk to file server and insert it into the file server floppy drive.~~

~~3. Select File, Get From, Floppy disk after logging onto the DASH2 file server.~~

~~4. Copy the ABPM files to the ABPM subdirectory under the SITEWORK directory. The new ABPM files will be transfered overnight.~~

~~5. Remove floppy disk from the file server floppy drive.~~

Section for ABPM Trainers Only:

ABPM Training and Certification of Clinical Center Trainers

Ambulatory blood pressure monitoring (ABPM) provides objective measurement of blood pressures for a specified period of time (e.g., 24 hours). However, in order to obtain accurate ABPM readings, placement must be done in a correct and consistent manner. Therefore, all staff responsible for placing ABP monitors must be trained and certified in proper ABPM placement procedures.

Each center must have a trainer for ABPM who will be responsible for ensuring certification of staff involved in ABPM placement. Each ABPM trainer will be re-certified centrally at the annual training session.

Before training and certification (or recertification), trainees should read the MOP Chapter on ABPM (Chapter 20).

The DASH2 study trainer will certify and re-certify all site trainers. This trainer will review 1) proper equipment use, 2) use of SpaceLabs software for uploading and downloading monitors, and 3) DASH2 study criteria. He/she will demonstrate ABPM placement, illustrating exactly what needs to be done and which DASH2 forms need to be used. The leader will observe each sites' trainer place two monitors on subjects and will observe their adherence to the DASH2 protocol. In addition, all of the sites' trainers must correctly download the monitors and create appropriate computer files (according to the DASH2 protocol). Finally, the trainers will be required to successfully complete the written exam.

Training and Certification of Technicians at individual centers:

Once certified, site trainers may certify technicians at their individual sites using the same criteria required for their certification. The trainees need to review MOP Chapter 20(Ambulatory Blood Pressure Monitoring). In addition, the trainers will need to review the following procedures with their site's staff.

1. Proper equipment use.
2. Demonstrating proper ABPM placement procedures.
3. Uploading and downloading monitors using SpaceLabs computer software.
4. Transferring completed data to fileserver.
5. Determining a successful ABPM session based on DASH2 criteria.
6. Creating appropriate transfer file.

Study Forms required for Certification/Recertification of ABPM

1. ABPM Placement Form (Form #27)
2. ABPM Participant Questionnaire Form (Form #28)
3. ABPM Initialization Checklist/ Downloading Checklist/ Transfer Checklist Form (Form #59)
4. ABPM Instructions to Participants (Form #60)
5. ABPM Certification Written Test (Form #61)
6. ABPM Certification Form (Form #62)
7. ABPM Observation Checklist Form (Form #70)

Certification/Recertification Criteria

The trainees will need to successfully complete the following to be certified:

1. Pass an ABPM certification written test (Form #61), which includes review of ABPM data on the SpaceLabs computer software to ensure that trainee can appropriately assess whether specified ABPM measurements meet DASH2 criteria.
2. Observed placement of ABPM device on two patients. Trainer should make sure that technician uses each ABPM form appropriately and follows all steps outlines in the MOP chapter on ABPM. Also, the trainee must correctly download monitor's data to the desktop P.C.
3. Wear an ABPM successfully for a 24-hour period (optional, but highly desirable).

All technicians will need to be re-certified every 6 months. The criteria for recertification is the same as the certification criteria. After the technician has successfully completed the certification, the completed forms need to be entered into the certification system on the DASH2 file server (see the Certification User's Manual for details). The completed certification written test (Form #61), completed certification form (Form #62) and the completed Observation Checklist form (Form #70) must be sent or Faxed to the Coordinating Center (Attn: Reesa Laws) for review. Each site must maintain records on who is certified for ABPM placement, and the date they were certified. The Coordinating Center will also keep records on certification.

Certification for ABPM Placement Only

Sites may choose to certify staff in ABPM placement only. The trainees need to review MOP Chapter 20 (Ambulatory Blood Pressure Monitoring). In addition, the trainers will need to review the following procedures with their site's staff.

1. Proper equipment use.
2. Demonstrating proper ABPM placement procedures.

Study Forms required for Certification/Recertification of ABPM Placement Only

1. ABPM Placement Form (Form #27)
2. ABPM Instructions to Participants (Form #60)
3. ABPM Certification Written Test (Form #61)
4. ABPM Observation Checklist Form (ABPM Placement Only)(Form #99)

Certification/Recertification Criteria for ABPM Placement Only

The trainees will need to successfully complete the following to be certified:

1. Pass an ABPM certification written test (Form #61).
2. Observed placement of ABPM device on two patients. Trainer should make sure that technician uses each ABPM form appropriately and follows all steps outlines in the MOP chapter on ABPM.
3. Wear an ABPM successfully for a 24-hour period (optional, but highly desirable).

All technicians will need to be re-certified every 6 months. The criteria for recertification is the same as the certification criteria. After the technician has successfully completed the certification, the completed forms need to be entered into the certification system on the DASH2 file server (see the Certification User's Manual for details). The completed certification written test (Form #61) and the completed Observation Checklist form (Form #99) must be sent or Faxed to the Coordinating Center (Attn: Reesa Laws) for review. Each site must maintain records on who is certified for ABPM placement, and the date they were certified. The Coordinating Center will also keep records on certification.