

AASK COHORT MANUAL OF OPERATIONS

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CHAPTER 1. CLINIC MANAGEMENT

1.1 Recommendations for Space

Office, storage, and patient care space will be different at each clinical center. Adequate space to see participants, to complete and store forms, to file or store participant records, and for private workspace for team members must be available. Thus the goal is to have organized and efficient use of available space to facilitate successful implementation of the study.

Each clinical center will need space for the following:

1.1.1 Patient Care Space

Many clinical centers will have the use of an outpatient clinic, hospital facility, or Clinical Research Center (CRC). If possible, the patient care area should be convenient for participants and near a parking facility and/or public transportation. A room that is quiet and free of distractions must be available for blood pressure measurements. A private and quiet room is necessary for examinations and counseling. A centrifuge for spinning blood, a refrigerator to store blood and urine samples, a work table/counter with sink for handling and processing blood and urine samples, and an area for storing laboratory supplies and data forms should be in or near the patient care area. It would be helpful to have the pharmacy nearby if medications are stored with the pharmacist. Team members will need work space for forms completion and/or technical duties while seeing participants in the patient care area.

1.1.2 Office Space

Adequate space should be available for team members to conduct their work when they are not with study participants. Privacy for phone calls with study participants and for participant conferences is essential. A room to conduct study team meetings should be available. A copy machine, FAX, and computer should be nearby.

1.1.3 Storage Space

Space must be available for participant records, data collection forms, medications, and office and laboratory supplies. A file cabinet which can be locked should be convenient to store medications and participant records.

1.2 Recommendations for Supplies/Equipment

The Study Coordinator or designated person will be responsible for ordering and maintaining an inventory of supplies sent from the central facilities and those purchased or obtained locally. Supplies will include office and laboratory supplies as well as data forms.

1.2.1 Office Supplies/Equipment

Office supplies such as xerox paper, pens, pencils, water proof markers, staples, labels, notebooks, dividers, file folders, computer maintenance supplies, etc. should be readily available.

1.2.2 Laboratory Supplies/Equipment

Supplies for laboratory functions, processing, and handling should include items from the following list that is comprehensive but not inclusive: urine collection equipment for participants (jug or other collection container, speci pans, and triangular containers); cylinders for measuring urine (250 mL and 1000 mL or 2000 mL); vacutainer needles and holders, butterflies, and leur locks (or heparin lock) tourniquets and rubber gloves; 3 and 12 mL syringes; gauze, cotton balls, bandaids, alcohol wipes; 9.5 ml serum separator tubes; 7 ml EDTA tubes; 30 ml polypropylene urine mailing tubes; 15 ml polypropylene serum mailing tubes; routine urinalysis conical tubes; tape; armboards (optional); biohazard garbage liners and Sage Sharps disposables; Fed Ex pouches, ziplock plastic bags, mailing box and styrofoam insert, ice packs, (reusable polar or freezer packs), glacial acetic acid, saline, and heparin; thermometers; Pasteur pipettes; pH test paper; distilled water or deionizer cartridge; pregnancy test kits (see below); a champ wrap (optional); and a pill count tray.

1.2.3 Blood Pressure Equipment

Each clinical center will need two Tycos Classic Hand Aneroid sphygmomanometers, two blood pressure bulbs and control, blood pressure tubing, a dual teaching stethoscope, and a variety of cuff sizes (pediatric, adult regular, adult large, and thigh), mayo stand or patient bedside adjustable tray holder, weight scale, and a chair with a back on it.

1.3 Scheduling of Activities

A system and an organization that will facilitate the orderly and efficient management of multiple activities including administrative, patient care, data management, and quality control must be developed. The Study Coordinator will be in charge of these activities but has the authority to delegate when appropriate to team members.

1.3.1 Administrative Activities

These activities include: 1) securing adequate space, equipment, and supplies for study needs; 2) developing a working relationship with liaisons such as pharmacist, clinic and/or CRC non study staff, and personnel from pathology, local laboratory, ECG lab, medical records, participant registration, and billing/accounting; 3) ordering and maintaining a supply and the storage of study medications; 4) communicating with referring physicians about participant test results and updates; 5) coordinating study activities with consortium institutions, if appropriate; 6) scheduling clinic appointments that are compatible with the participants, staff schedules, and clinic/CRC schedules and available space; and 7) arranging

for reimbursement for participation fee and/or fee for parking and transportation. The liaison personnel must be informed about the study goals and provide information about the procedures pertinent to their role in the study. The Study Coordinator will notify team members of AASK activities and facilitate study related communication and problem solving. Team meetings should be scheduled at least on a monthly basis and more when needed. The Study Coordinator will be responsible for ensuring that Protocols, Manuals of Operations, and data forms are current. Every effort should be made to create a clinic setting in which workspace, workloads, and communication will facilitate conducting the trial as efficiently and effectively as possible.

1.3.2 Scheduling Participant Visits

During all phases of the study, special emphasis should be placed on adhering to the participant's target visit window. Participants should be scheduled, if possible, at their convenience but also at a time that is compatible with team and other clinic/CRC activities. Phone calls and/or reminder cards are encouraged to promote adherence to appointments. When visits are missed, attempt to reschedule immediately for an appointment within the window. Special attention should be given to interim visits, making sure participant and staff are aware of these "non routine type" visits.

1.3.3 Quality Data Collection

The Study Coordinator will review all data forms for completeness and accuracy and to ensure timely submission to the Data Coordinating Center. The procedure for mailing blood and urine samples will be coordinated with the Study Coordinator and technical personnel to ensure prompt shipment to the Central Labs. The Study Coordinator or designated person will monitor and ensure the calibration of blood pressure equipment. Data forms will be filed in an area convenient for study personnel's access. Prior to each visit, appropriate forms will be assembled, headed, and distributed to designated personnel. To ensure that the study has quality data, team members must know the purpose of the study, the protocol design, and the sections of the Manual of Operations that are pertinent to their roles in the study. If protocol expectations and study goals are clear and common to all team members, then protocol adherence by staff will help ensure quality data collection and a pleasant working environment.

1.4 AASK Reference Materials

1.4.1 Reference Materials

Each center should maintain three hole-punched copies of the Protocol, Manual of Operations, Forms Manual/Forms Usage Instructions, and Address Directory.

1.4.2 The Paper Copy of the Medication Logbook

The DCC also distributed one paper copy of the Medication Logbook, NDC Codes, to each center. The paper copy is bound and will not be updated. Updates appear in the computer.

CHAPTER 2. PATIENT VISIT MANAGEMENT

2.1 Preparation Before Participant Visits

2.1.1 Reminder About Appointments

The Study Coordinator or designated personnel should remind participants about each scheduled or interim clinic visit either by phone or by card. Calling prior to the scheduled visits provides an opportunity to determine how the participant feels, if the participant has any questions, or if the participant has had any intercurrent illnesses. Reminding the participant about the activities that are planned for the next visit as well as estimated time for clinic visits is helpful. Reminders to bring medications, to fast and bring urine collection when appropriate, will hopefully foster improved compliance.

Participants should be encouraged not to miss visits, but if missing a visit is necessary, the participant should call and reschedule as soon as possible. If the patient doesn't call, the clinic staff should call him or her within 24 hours to reschedule the visit. If there is still no contact with the patient within 3-4 days a letter requesting the patient to call should be sent to the patient.

2.1.2 Assemble Materials for a Visit

Prior to each visit, the Study Coordinator or designated personnel will assemble the forms, lab supplies and requisitions, and the mailing materials appropriate for that visit. The forms should be headed with the participant's ID number and name code. The forms and laboratory tests (central and local) required for each visit are found in the Forms section of the Manual of Operations. Assembling the materials used for mailing will facilitate prompt shipment to the central laboratories for processing. Urine jugs prepared with an instructional label and with the addition of acetic acid will be given to participants on the visits prior to 24-hour urine collection.

2.1.3 During the Visit

It is important for staff to be pleasant, organized, and on time for clinic visits. Blood pressure measurement, pill counting, and issuing additional medications will be central to each visit. Participants should be given a calendar or appointment card for their next scheduled visit.

2.2 Follow-Up After the Visit

2.2.1 Following the Visit

Promptly complete and key enter the required forms. Send laboratory samples to the appropriate facilities in a timely manner; inform team of participants' test results; inform participants and referring physicians of tests results; schedule interim visit if necessary; and remind participant of next scheduled appointment before clinic appointment.

CHAPTER 3. BASELINE VISIT

3.1 Overview

The AASK Cohort Study is a prospective, observational study that is an extension of the AASK clinical trial. The AASK trial was a randomized, clinical trial that tested the effects of 3 different medications used as first line antihypertensive therapy (ramipril, metoprolol and amlodipine) and 2 levels of blood pressure control (usual control and more aggressive control). Of the 1,094 randomized participants in AASK, we anticipate that 650-750 individuals who have not reached ESRD will enroll. In addition, those individuals who reached ESRD during the AASK trial will be invited to attend one visit for collection of DNA. Twice each year, approximately every 6 months, exposures will be collected. Exposures will include environmental, genetic, physiologic, and socio-economic factors. The primary renal outcome will be a clinical outcome defined by doubling of serum creatinine, ESRD or death. Appropriate antihypertensive treatment (medications and target BP level as determined in the AASK trial) will be provided to all participants who do not have ESRD. In this fashion, the cohort will directly control two of the major ‘known’ determinants of kidney disease progression (treatment of hypertension and use of reno-protective, antihypertensive medication) and will therefore address research hypotheses in the setting of recommended antihypertensive care. We anticipate a minimum of 4 contacts and maximum of 6 contacts for BP control. The minimum duration of follow-up in the Cohort Study will be 5 years (total of 10-12 years, including the period of the AASK trial).

The baseline visit is critical in obtaining accurate information to maximize the validity of the follow-up data during the cohort study. Correct measurement of baseline parameters is of the utmost importance to the success of this study because it is the foundation against which we determine all study outcomes. In addition the attention to detail in the collection and recording of the baseline data sets the tone for the conduct of the study throughout the entire period. It is essential that the procedures described below for collecting and recording baseline parameters be followed exactly. Precision is essential for valid comparisons of future exposures within the cohort across time.

3.2 Background

Experience in providing training support for AASK study coordinators to help them achieve and maintain a high standard of clinical research performance (e.g. BP measurement, patient questionnaire/survey administration, sample collection and processing) has been a potentially valuable by-product of the AASK study. This training activity was necessarily an integral aspect of AASK. This section will provide a guideline for the complete set of parameters and the appropriate timelines for their collection to be obtained during the baseline period. Many of the specific details for these parameters (e.g. blood pressure measurement, sample processing, cardiovascular procedures) are discussed in more detail in their respective sections of the manual of operations.

3.3 Baseline Procedures; Step by Step

3.3.1 Overview

Contact Pattern and Data Collection Elements: The purposes of the baseline visits are to collect exposure data at the initial period of the cohort study. The types of data to be collected at baseline include patient questionnaire/survey responses (exposures and clinical event surveillance), blood pressure, limited physical exam including height/weight, electrocardiogram, blood, 24-hour urine, finger nails clippings, ambulatory blood pressure monitoring and echocardiography.

For those persons who have not reached ESRD, Table 2 displays the baseline data collection items and procedures by visit during the first two years.

For those persons who reach ESRD during the cohort, Table 3 displays the data collection items and procedures by visit during the baseline ESRD period.

3.3.2 Eligibility/Inclusion Criteria

The only inclusion criteria for the AASK Cohort will be prior randomization in the AASK trial and written informed consent, specific for the Cohort study (see Section 3.4 below).

3.4 Informed Consent

3.4.1 General Principles

In order to participate in the study, each participant must provide written informed consent, specific for the AASK Cohort study. A copy of the institutional IRB approval for the AASK cohort study, and a copy of the signed consent form are mandatory prior to proceeding with the baseline procedures. This will document the agreement of the participant to participate in the study activities.

3.4.2 Participation in Other Studies

Participants will be encouraged by AASK Study personnel to not participate in any other research studies during their participation in the AASK Study unless it is an AASK ancillary study reviewed by the Publication, Ancillary Studies and Recruitment Subcommittees and approved by the Steering Committee.

3.4.3 Sequence of Procedures

It is recognized that Clinical Center Institutional Review Boards (IRBs) have official responsibility for determination of informed consent procedures. Prototype informed consent forms have been developed for the study, and each Clinical Center's IRB-approved consent form will be reviewed to make sure the essential material is

included. The following description is intended as a guideline that most centers could follow.

- 1) Consent should be obtained at the time of the Baseline Visit, and will include description of the interaction with members of the study team, measurement of data including physical examination, blood pressure measurement/management, survey instruments, blood and urine tests. 2) Consent for the other stages of the study (DNA collection) may be obtained separately or combined into a single form.

3.4.4 Privacy

At the beginning of the study, each participant is assigned an identification number and a name code. Participants are identified only by number in any individual tabulations, and it is expected that only group data will be published. If individual participant data are published, no identifying information will be included. The medical records of participants in the AASK Cohort Study will be confidential. Specific study related information may be made available to the Food and Drug Administration, the study sponsors, and National Institutes of Health.

3.5 Data Collection

3.5.1 History and Physical Examination

A limited history and physical examination may be performed during baseline. Blood pressure and weight will be reported. All other information that is not reported on the forms should be documented in the patient's chart.

3.5.2 Blood Pressure Measurement

Blood pressure will be measured in a standardized fashion by an AASK trained and certified observer using an aneroid device. Three consecutive seated readings will be recorded with the mean of the last two readings documented as the clinic visit measurement. While the general approach to blood pressure measurement will be identical to that used in the AASK trial, we decided against continuation of the random-zero device in the Cohort because the American Hospital Association and the Environmental Protection Agency have proposed to eliminate mercury from hospitals. A detailed procedure for BP measurement is provided in Chapter 6 of this MOP.

3.5.3 BP Management

AASK participants who have not reached ESRD will be encouraged to have their BP managed by AASK Cohort investigators and staff. The recommended approach to hypertension control is based on the results of the AASK trial. In the AASK cohort study the primary goals of hypertension management will be to achieve a systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg using maximally tolerated dose of ACEI as first line therapy. If either the systolic blood pressure is > 140

mmHg or the diastolic blood pressure is > 90 mmHg notify the AASK PI or co-investigator to initiate appropriate recommendations.

Table 1 below summarizes the recommended approach to medications in the AASK Cohort Study. A detailed procedure for BP management is provided in Chapter 5 of this MOP.

Table 1
Recommended Drug Titration Approach for the AASK Cohort

First line	Ramipril (maximum dose of 20 mg/day) [ARB for those who develop an ACEI cough]
Second line	Furosemide or HCTZ
Third line	Verapamil (Covera-HS) or Beta-blocker (Carvedilol)
Fourth line	Amlodipine (Norvasc) or Clonidine pills or Clonidine TTS or Reserpine or Diltiazem (Tiazac)
Fifth line	Hydralazine, Doxazosin/other α -blocker or Minoxidil

3.5.4 Participant Questionnaires/Surveys

Questionnaires will be administered that focus on potential exposures of interest and on surveillance for outcomes (ESRD and cardiovascular outcomes). Any symptoms of hypotension and any new symptoms volunteered by participants since the last visit will be recorded at each visit. The checklist on Form 111 will be used to record the responses. Reasons for missed visits will also be documented on Form 111.

Baseline information regarding participants' quality of life will be elicited using Forms 180, 186, 187, 190 and 191.

3.5.5 Medications

At the baseline visit the types of antihypertensive medications and types of other concurrent medications will be collected using procedures developed in AASK. During the baseline visit, many of the participants may be taking a variety of medications including antihypertensive agents as well as drugs for other indications. During the baseline visits, the Clinical Center study team will review the indications for all prescribed medication and record all medications. This includes both prescribed and over-the-counter medications.

3.5.6 Serum and Plasma Chemistries

Samples will be shipped to the Central Laboratory of the Cleveland Clinic within one week of collection. Details on sample shipment are in MOP Chapter 9. Certain serum tests may also be done locally for patient care and patient safety reasons. Local analysis can provide a quick turn around, when results are needed rapidly.

Serum: Sodium, Potassium, Chloride, Bicarbonate, Urea Nitrogen, Glucose, Creatinine, Total Protein, Albumin, Aspartate transaminase (AST), LDH, Alkaline Phosphatase, Total Bilirubin, Calcium, Phosphorus, Uric Acid, Magnesium, GGT, Insulin.

Plasma: To be determined

Local CBC: WBC, RBC, Hemoglobin, Hematocrit locally

3.5.7 24-Hour Urine Collections

Participants will collect a 24-hour urine. The urine should be mixed, measured and aliquoted and must arrive at the Central Laboratory within one week of collection. Detail on sample collection and shipment are located in MOP Chapter 9.

The AASK Research Technician or Study Coordinator will complete the Urine Mailing Form #123. Participants will be queried about the completeness and accuracy of each urine collection. It is important to ascertain whether the urine collection is accurate and complete (i.e., if the participant remembers to discard the first urine sample and collect all of the urine for the next 24 hours). Otherwise, the urine should not be sent to the Central Laboratory, and the participant should collect another urine.

Urine: creatinine, protein, albumin, sodium, potassium, and urea nitrogen

3.5.8 Finger Nail Clippings

At the baseline visit, fingernails will be collected. Participants will be asked to trim each of their 10 fingers with a chromium-free nail clipper (to be provided) and will be asked to put the clippings in a labeled plastic bag. Form 168 will be completed and key entered. The bags will be stored at room temperature and then shipped to the Central Laboratory of the Cleveland Clinic.

3.5.9 Electrocardiogram

At the baseline visit an ECG will be obtained. The ECG readings are to be obtained to document the participant's status and for participant safety. A copy will be retained for local use and the original sent to the Cardiovascular Research Foundation (CRF) at Lenox Hill Hospital in New York City for central coding.

3.5.10 Echocardiography

At baseline a “limited” echocardiogram will be obtained to measure left ventricular mass. This 2-dimensional-directed, M-Mode echocardiogram will record LV septal thickness, LV posterior wall thickness and LV dimensions (separately, during systole and diastole). The procedure for performing and handling echocardiogram results is detailed in MOP Chapter 11.

Any additional questions should be referred to the CRF at Lenox Hill Hospital (see MOP Chapter 11).

3.5.11 Ambulatory BP Monitoring

At baseline a 24-hour ambulatory blood pressure recording will be obtained. The study will use the SpaceLabs™ 90217 Ultralite or SpaceLabs™ 90207 devices. Make certain your center has or has access to one of these approved devices. Each center should have an AASK team member who has been oriented to performing 24-hour ambulatory blood pressure recording. The procedure for performing and handling 24-hour ambulatory blood pressure recording is detailed in MOP Chapter 13.

3.5.12 DNA

DNA will be collected once, most likely during the baseline period. The timing of the collection will depend on the capacity of the AASK Genetics Core Laboratory (Mt. Sinai Hospital) to process specimens. The patient must have signed a written consent for DNA collection. Blood will be shipped to Core Laboratory by overnight mail. When received, blood will be divided into 3 aliquots: 10 ml will be used to isolate genomic DNA; 10 ml will be used either to immortalize lymphocytes or for controlled freezing of 4 aliquots of purified PBMC; approximately 50 ul will be spotted onto IsoCode Stix (Schleicher & Schuell) and dried as an archive for future DNA isolation/sample identification/quality control. The procedure for DNA collection is detailed in MOP Chapter 7.

Table 2. Check off list to ensure complete collection of all baseline data elements for those patients who have not reached ESRD.

Baseline Data Collection Check-Off Form	C-0
Informed Consent	
Contact Information	
Enrollment Form (Form 81)	
Blood Pressure Measurement (Form 110)	
Weight (Form 110)	
Questionnaire (Forms 84, 85, 180, 186, 187, 190, 191)	
Medication Questionnaire (Form 140)	
- Antihypertensive Meds	
- All Other Medications	
Fasting Blood (must fast at least 10 hours): (Form 122)	
- 2 Red Tops*: Creatinine Lipids, Glucose, Insulin, Routine Chemistry	
- 1 EDTA Lavender Top for Local CBC - 1 EDTA Lavender Top for CBL	
Blood for DNA (Form 120)	
CBC (Form 113)	
24-Hour Urine (Forms 123, 125)	
Finger Nail Clippings (Form 168)	
Electrocardiogram (Forms 114, 115)	
Ambulatory BP (Forms 170, 171, 173)	
Echocardiogram (Forms 117, 119)	

*Use 10ml Red Top or 9.5ml SST (Red/Gray Speckled Top)

Please note a 9.5 ml serum separator tube, when filled, will yield approximately 4mls of serum.

3.6 Collection of Data upon the Initiation of Renal Replacement Therapy

3.6.1 Overview

For participants who have enrolled in the Cohort Study who reach end stage renal disease (ESRD) and have begun renal replacement therapy (RRT), data will be recorded at annual visits to verify and update data collection elements, and update the method of RRT and if appropriate its frequency (cadaveric transplant, living related donor, hemodialysis and its frequency, peritoneal dialysis (CCPD, CAPD, other).

3.6.2 Procedure

For patients who reach ESRD the baseline data collection will be similar to those not on ESRD. The development of ESRD is associated with a significant change in serum chemistries, medications, and often clinical findings. Thus a re-assessment of many of the data collection elements is recommended at this time to establish a new “baseline”. The procedure is similar to those not on ESRD with the addition of collection of Renal Replacement Therapy (RRT) specific data (Form 128 and 129).

Table 3. Check off list to ensure complete collection of all baseline data elements for those patients who have reached ESRD during the Cohort Study.

ESRD Baseline Data Collection Check-off Form	C-0
Contact Information (collected locally)	
Questionnaire – Exposures (Form 85)	
Start of Dialysis/Transplant (Form 128)	
Status of Dialysis/Transplant (Form 129)	
Visit Form (Form 111)	
Medication Questionnaire (Form 140) - Antihypertensives - All other medications	
Laboratories (Form 122) - Lipids, Glucose, Insulin - Routine chemistry, including Ca/PO4	
CBC (Form 113)	
Finger Nail Clippings (Form 168)	
Electrocardiogram (Forms 114, 115)	
Echocardiography (Forms 117, 119)	

3.7 Telephone/Written Communications

Telephone inquiries having to do with aspects of sample collection/processing/mailing may be directed to the Central Biochemistry Laboratory. Calls to the Central Biochemistry Laboratory will be answered between 9:30 a.m. and 6:00 p.m. Eastern time, weekdays only.

Written inquiries can be forwarded to the Central Biochemistry Laboratory via the FAX number, 216-444-7004.

The Central Biochemistry Lab will communicate with participating clinical centers over electronic mail, fax, or at the addresses/phone numbers listed in the AASK Address Directory.

3.8 List of Some Common Medications That You Cannot Take 2 Days Before a 24-Hour Urine Collection Test or Serum Measurements

Refer to MOP Section 9, Appendix 3 for list of medications.

CHAPTER 4. FOLLOW UP VISITS

4.1 Routine Follow Up for Patients who enroll in the Cohort Study

Patients can enroll in the AASK Cohort Study beginning April 19, 2002. It would be ideal if all baseline data were completed by July 31, 2002. All Baseline data is labeled as C0.

Patients are seen every 3 months after Baseline. Patients may be seen more often if needed.

Below is an example of a visit schedule for a patient who was enrolled on May 13, 2002:

<u>Calendar Month</u>	<u>Month Number</u>	<u>Visit Number Label</u>
13-May-02 to 30-May-02	0	C0
01-Jun-02 to 30-Jun-02	1	C0
01-Jul-02 to 31-Jul-02	2	C0
01-Aug-02 to 31-Aug-02	3	C3
01-Sep-02 to 30-Sep-02	4	C3
01-Oct-02 to 31-Oct-02	5	C6
01-Nov-02 to 30-Nov-02	6	C6
01-Dec-02 to 31-Dec-02	7	C6
01-Jan-03 to 31-Jan-03	8	C9
01-Feb-03 to 30-Feb-03	9	C9
01-Mar-03 to 31-Mar-03	10	C9
01-Apr-03 to 30-Apr-03	11	C12
01-May-03 to 31-May-03	12	C12
01-Jun-03 to 30-Jun-03	13	C12
01-Jul-03 to 31-Jul-03	14	C15
01-Aug-03 to 31-Aug-03	15	C15
01-Sep-03 to 30-Sep-03	16	C15
01-Oct-03 to 31-Oct-03	17	C18
01-Nov-03 to 30-Nov-03	18	C18
01-Dec-03 to 31-Dec-03	19	C18
01-Jan-04 to 31-Jan-04	20	C21
01-Feb-04 to 30-Feb-04	21	C21
01-Mar-04 to 31-Mar-04	22	C21
01-Apr-04 to 30-Apr-04	23	C24
01-May-04 to 31-May-04	24	C24
01-Jun-04 to 30-Jun-04	25	C24

All visits after C0 have visit windows that are three calendar months long except for C3. The C3 window is only two months long to allow extra time for the C0 visit.

The target date for C6 visit requirements is November 13, 2002. Every visit done between October 1, 2002 and December 31, 2002 is labeled as C6. This three-month interval is the recommended window for C6 visit procedures.

If a visit is done between January 1, 2003 and March 31, 2003, the visit is labeled as C9.

The target date for C12 visit requirements is May 13, 2003. Every visit done between April 1, 2003 and June 30, 2003 is labeled as C12. This three-month interval is the recommended window for the C12 visit procedures.

If a visit is done between July 1, 2003 and September 30, 2003, the visit is labeled as C15.

4.2. Hospitalizations

Hospitalizations are documented on Form 111 (Visit/Missed Visit Form), question 37.

Hospitalizations are also documented by completing and entering Form 144 (Hospital Admission Notification Form) and Form 145 (Hospitalization Form).

The Cardiovascular Subcommittee will review all cardiovascular hospitalizations. Therefore, any blood tests, ECGs, labs, etc. that were done while the patient was hospitalized should be copied and sent to the DCC.

4.3 Deaths

All deaths should be documented by completing and entering Form 148 (Death Notification Form). The Death Certificate should be faxed to the DCC as soon as possible. Also, any blood tests, ECGs, labs, etc. (if the patient died while in the hospital) should be copied and sent to the DCC.

4.4 Dialysis or Transplant

For those patients who go on to dialysis or have a transplant, a Form 128 (Renal Failure Form) should be completed and entered. Form 129 (Follow-Up for Patients on Dialysis or Transplanted Form) should be completed annually.

4.5 Follow Up after Dialysis or Transplantation

Patients are seen annually according to their appointment schedule after they go on dialysis or are transplanted. However, an echocardiogram should be performed preferably within two months after dialysis begins.

The number of cardiovascular hospitalizations will be tracked using the ESRD Patient Hospitalization Form 141. Also, the CBL Serum and Plasma Mailing Form 122 will record the number of hours since the last dialysis start time. If a special frozen plasma

sample is not collected prior to dialysis, then it should be collected as soon as possible after dialysis begins using the CBL Dry Ice Mailing Form 127.

CHAPTER 5. BLOOD PRESSURE MANAGEMENT

5.1 Study Objective

The study objective will be to achieve a blood pressure goal of $\leq 130/80$. This blood pressure goal was the one determined to provide maximal renoprotection in this population. Centers are encouraged to assume responsibility for blood pressure management of all participants

The following medications will be provided by the study: ramipril, hydrochlorothiazide, furosemide, carvedilol, clonidine, reserpine, amlodipine, doxazosin, hydralazine, and minoxidil. **Every attempt will be made to obtain an angiotensin receptor blocker provided by a manufacturer for ACEI intolerant patients.** The order of drug addition will be left to the discretion of the investigator, but a reasonable sequence would be ramipril, HCTZ or furosemide (depending on whether estimated GFR is $>$ or $<$ 35 ml/min/1.73m²), carvedilol or other sympatholytic (reserpine or clonidine) if there is a contraindication to carvedilol, amlodipine, doxazosin, minoxidil/hydralazine. Prescription of these agents will be consistent with the dosage recommendations as outlined in the manufacturer's package insert.

Other antihypertensives may be utilized at the discretion of the investigator and/or participant's primary care provider. However, these agents will be provided by the study. In addition, to limit variability in outcomes related to drug selection, centers are encouraged to conform when possible to the treatment algorithm listed above. Conversion of participants to the recommended treatment algorithm should be accomplished within 6 months of starting the After AASK protocol.

Participants will be seen at three month intervals for BP management and data collection. Additional visits for participants who are not at their BP goal will be conducted by the centers as needed or coordinated through the participant's primary provider or Nephrologist. The numbers/percent of participants at each center who are above 130/80 and above 180/110 will be monitored and provided to all centers at quarterly intervals.

5.2 Data Safety and Monitoring Plan

Level of risk: We believe that the risks associated with participation in this observational protocol to fall in the low risk classification. The procedures to be performed include: history/physical examination, questionnaires, venipuncture, urine collection, nail clippings, ambulatory blood pressure monitoring, echocardiogram and electrocardiography. In addition, DNA analysis will be performed.

Mechanism of safety monitoring: We have developed a set of action items to prompt follow up action in order to ensure the safety of participants and to optimize their medical care. While this is an observational study, we believe that it is important and ethical to ensure that an abnormal physical finding, lab value or diagnostic test is appropriately followed up. These will be reviewed by the principal investigator or their authorized designee after each visit. In addition, a mechanism for reviewing hospitalizations, study

events, as well as clinical centers with unsatisfactory blood pressure control among its participants (> 30% of participants with blood pressure >140/90 on = two consecutive visits or systolic blood pressures > 180 or diastolic blood pressure >110) has been incorporated into the manual of operations.

Anticipated adverse events: The only anticipated adverse events include those associated with the diseases under study (hypertension and renal disease) and potential medication-related events. Adverse events will be graded according to Common Toxicity Criteria (CTC II) <http://ctep.info.nih.gov>. Attribution of events will be made by the principal investigator as related, possibly related, or definitely related.

Reporting and review of adverse events: Adverse events will be reported to Data Coordinating Center for review and classification by the appropriate study subcommittee and forwarded for review by the NIH and its appointed data and safety monitoring board. Although the investigative team will oversee management of blood pressure, response to non-emergent treatment and disease-related events will be coordinated and mediated through the participant's primary care physician. If the participant does not have a primary care physician, every effort will be made to facilitate care within our healthcare systems.

5.3 Blood Pressure

The goal of blood pressure management will be consistent blood pressures \leq 130mmHg systolic and \leq 80 mmHg diastolic. While management of blood pressure by the AASK clinical center is not required for participation in the AASK Cohort Study, this is strongly encouraged. The rate of BP control in AASK Cohort participants at each center will be monitored by the study. The percent of participants at each center with BP's < 140/90 and those with stage 2 or higher BP's will be provided to the centers quarterly. In addition, participants with > stage 3 blood pressures at 2 consecutive visits centers will be referred to the Clinical Management Subcommittee as will centers with > 30% of participants with > 2 consecutive blood pressures > 140/90. Summary data will be also reviewed along with other safety data by the DSMB.

CHAPTER 6. BLOOD PRESSURE MEASUREMENT

6.1 Overview of Blood Pressure Measurement

In the AASK Cohort Study, sitting and standing blood pressure is measured at every visit in a resting state, using three sitting measurements and one standing measurement with a Tycos Classic Hand Aneroid sphygmomanometer. The Tycos Classic Hand Aneroid has been chosen because of some institutions concerns with the safety of mercury sphygmomanometers.

Correct measurement of blood pressure is of the utmost importance to the success of this study since the study will determine prospectively the long-term course of kidney function and risk factors for kidney disease progression in African Americans. It is essential that the procedures described below for measuring blood pressure be followed exactly. Precision is essential for valid blood pressure measurements since the Cohort Study will directly control two of the major 'known': determinants of kidney disease progression (treatment of hypertension and use of reno-protective, antihypertensive medication) and will therefore address its research objectives in the setting of recommended antihypertensive care.

6.2 Background

Experience in providing training support for blood pressure observers, to help them achieve and maintain a high standard of measurement performance, has been a potentially valuable by-product of the nation-wide Hypertension Detection and Follow-up Program (HDFP)¹ and the Systolic Hypertension in the Elderly Program (SHEP)². This training activity was necessarily an integral aspect of HDFP, SHEP and AASK. However, the measurement problems addressed in these Programs were not unique, and the solutions formulated by the investigators of these trials may therefore be helpful to others who encounter some of the same problems in planning detection and/or follow-up procedures for high blood pressure.

In this spirit, we present to the AASK Cohort investigators the essential components of the HDFP/SHEP and AASK training and certification programs for blood pressure observers and the recommendations from the American Heart Association in using a proper blood pressure procedure. These components include the step-by-step procedures for use of the Tycos Classic Hand Aneroid sphygmomanometer; brief lecture/slide presentations for initial orientation of trainees; and the training/certification procedure developed for the HDFP, adapted for the SHEP, AASK, and now adapted for use in the AASK Cohort Study including a videotape test for the quantitative assessment of individual observers' measurement performance. The actual scoring for this videotape test and its procedures will be conducted by the Data Coordinating Center.

It should be noted that other reference materials are available which blood pressure observers would be well advised to consult. Foremost is the American Heart Association booklet, "Human Blood Pressure Determination by Sphygmomanometry" (the latest edition is by Perloff, et al 1993)³ (a copy is attached) which has long been regarded as a standard reference on the subject. In addition, a 1978 publication by Prineas (Blood Pressure Sounds:

Their Measurement and Meaning - A Training Manual)⁴ provides a comprehensive discussion of the problems in blood pressure measurement as well as an extensive bibliography.

6.3 Training and Certification

High quality blood pressure readings are fundamental to any sound program measuring and controlling blood pressure levels.⁶⁻⁸ Yet many factors, including influences of the subject, the observer, the equipment, and the circumstances of measurement, work against the attainment of this basic objective. Thus, good results cannot be taken for granted and special attention must be focused on blood pressure measurement procedures and regular (every 6 months) calibration checks of the hand held Tycos Classic Hand Aneroid manometers.

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. Recertification will be required at six-month intervals for the duration of an observer's service in the AASK Cohort Study.

The AASK Cohort certification process includes training and the successful completion of:

- * a written test (every 6 months)
- * a live evaluation (every 6 months)
- * a videotape test (every 6 months)

The training strategy adopted by AASK Cohort is a two-stage program.

Before the program begins, each Clinical Center will identify one specific Training Supervisor for that clinic. The Training Supervisor must have at least 6 months prior experience in taking blood pressures. The Training Supervisor from each clinical center will be asked to demonstrate the blood pressure procedure at annual meetings. The Training Supervisors are responsible for performing a live evaluation on all staff members who are certified at their clinical center at the time of certification and every six months. Each center should have at least two staff members who are certified in blood pressure measurement.

The first stage of the program is the successful completion of the videotape test provided by Shared Care Research and Education Consulting, Inc. Shared Care will send these tests to the clinical centers every six months. The Blood Pressure Supervisor must take this test as well as each Blood Pressure Observer at the center. The Blood Pressure Supervisor and the Observer(s) must successfully complete this test at the time of certification and every six months.

The center will have 10 working days from the day the videotape test is received from Shared Care. During this time, each staff member who will be taking blood pressure measurements for the Cohort must successfully complete this test.

In this second stage, each Blood Pressure Supervisor will be asked to perform a live evaluation at Annual Meetings. The Blood Pressure Supervisor is then responsible for

completing the “Live Blood Pressure Reading Performance Evaluation” checklist (see Section 6.7.6 of this chapter) and two y-tube readings on each staff member who will be measuring blood pressure at each center every six months. An Observer will be responsible for completing the “Live Blood Pressure Reading Performance Evaluation” on the Blood Pressure Supervisor as well every six months. Each staff member measuring blood pressure must also complete a written test provided by the DCC. The center will fax the “Live Blood Pressure Reading Performance Evaluation” checklist and written test to the DCC.

The clinical center should fax the Shared Care confirmation sheet to the DCC showing that each staff member has successfully completed the videotape test.

The DCC is responsible for identifying who is a certified AASK Blood Pressure Observer. The Data Coordinating Center will, in addition, remain responsible for overall monitoring and quality control (as will be described in Section 6.7).

6.4 Blood Pressure Measurement Step By Step

6.4.1 Overview

In this chapter, the step-by-step procedures for blood pressure measurement in the AASK Cohort are presented. It should be emphasized that the steps outlined here can satisfactorily be followed for the vast majority of adult subjects participating in ambulatory follow-up. Exceptional situations do arise, with sometime serious obstacles to successful blood pressure measurement. The training program for a particular setting must include guidelines for handling such exceptions. Only a few will be noted. It will be the responsibility of the Training Supervisors in the Clinical Centers and in the Data Coordinating Center to encourage observers to note exceptional circumstances and to seek consultation with the Blood Pressure Consultant at the DCC when they arise so that participants will be appropriately evaluated. The Tycos Classic Hand Aneroid sphygmomanometers are used for blood pressure measurement for all AASK clinic visits and for the determination of peak inflation levels. This manual will concentrate on this device.

It should be noted also that the procedures listed here are illustrated in the third lecture presentation, "Procedures in Blood Pressure Recording" (Section 6.5.6).

6.4.2 Preparation for Blood Pressure Measurement

Some of the many extraneous factors influencing blood pressure are controlled by standardizing the measurement technique and the environment in which the measurement is made. Uncontrolled factors (time of day, identity of the observer) are recorded, so that they can be taken into account during analysis.

AASK patients must abstain from caffeine, smoking, and exercise at least one-half hour prior to and until completion of the blood pressure measurement. Current drug intake, including medications affecting blood pressure and non-prescription drugs, is recorded on the day of the examination.

Try to keep the blood pressure measurement as pleasant as possible. Patients should be given full explanation and instructions about the preparation for the blood pressure examination and an opportunity for brief questions. The setting in which blood pressure measurements are made will be standardized, and should take place in a separate, quiet room where no other activity is taking place, and where temperature fluctuations are minimal. Scheduling procedures should try to establish consistent appointment times to minimize as much as possible the impact of daily blood pressure variation. Equipment (including study forms, sphygmomanometer, etc.) should be checked and waiting for the participant.

Allow five minutes of rest in this quiet room after arm measurement and calculation of corrected peak inflation level but before pulse is measured which occurs prior to taking the blood pressure. Explain to the participant that the five-minute rest period will provide for more valid blood pressure measurements. Preferably, at this time, the observer should leave the room. The participant should be relaxed, seated with back supported with legs uncrossed and feet comfortably flat on the floor, not dangling. The patient should also be instructed to refrain from using a cell phone.

6.4.3 Blood Pressure Measurement Procedures

The sitting arm blood pressure is measured three times at each clinic visit. It takes approximately 10 to 15 minutes to make three blood pressure measurements including the initial five-minute rest.

Blood pressure equipment should be checked prior to seeing the patient. Once a participant is given instructions and explanations blood pressure measurement begins. The following steps must be followed precisely. The procedure is described here employing the AASK Cohort Blood Pressure Form 110.

A Blood Pressure Form 110 should be completed on the same day that an ABPM is placed.

All blood pressure measurements conducted by AASK Cohort Study Personnel on AASK patients must be recorded in the database, regardless of the clinical condition of the patient at the time of the measurement. This includes blood pressure measurements taken at home or other sites.

If more than one blood pressure measurement is obtained on the same patient on the same day, then:

- 1) Form 110s must be completed for each blood pressure measurement that is taken
- 2) The Form 110 for the FIRST blood pressure must be keyed by the center into the AASK database
- 3) Form 110s for all additional blood pressure measurements recorded on the same day should be faxed to the DCC

- 4) The complete AASK protocol for blood pressure measurements must be followed for each measurement

All blood pressure measurements taken by AASK personnel should be done by the Tyco Classic Hand Aneroid sphygmomanometer.

Blood pressure measurements conducted by AASK Cohort Study personnel on AASK patients should be conducted at the AASK Cohort clinic or a satellite office if at all possible. This applies both to protocol and interim visits.

Details:

- A. In exceptional circumstances blood pressure measurements may be conducted outside the AASK Cohort clinic or satellite office (e.g. at the patient's home or work), but the frequency of such measurements should be kept as small as possible.
- B. An item on Form 111 will capture the location of all visits, so that for some analyses in-home blood pressure measurements can be assessed separately from measurement conducted in the AASK Cohort clinics.

6.4.4 Stethoscope

A standard Littman stethoscope (or other comparable stethoscope) with a bell is used. Korotkoff sounds are best heard with the bell because of their low pitch. Stethoscope tubing should be about 12 to 15 inches from the bell piece to "Y" branching. This length provides optimal acoustical properties and allows the observer to read the sphygmomanometer at eye level and in a comfortable position. Earpieces should fit comfortably and snugly in the ears. Four points should be observed in using the stethoscope.

1. The earpieces should be directed forwards into the external ear canal.
2. The earpieces should be tight enough to exclude outside sound but not so tight that they cause discomfort.
3. The valve between the bell and the diaphragm should be turned in the direction of the bell.
4. The bell of the stethoscope should be placed lightly on the skin overlying the brachial artery - immediately below, but not touching, the cuff. The brachial artery is usually found above the crease of the arm, slightly towards the body. 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 a murmur can be heard which may prolong the apparent duration of fourth-phase Korotkoff sounds.

6.4.5 Arm Measurement and Cuff Sizes

The proper cuff size must be used to avoid under- or over-estimating the correct blood

pressure. Welch Allyn V-Lok cuff sizes are used in the AASK Cohort Study. To determine the proper cuff size, the observer must measure the arm circumference at the midpoint of the arm at each visit. This measurement is taken on the right arm that has been bared from the shoulder. With the participant standing, holding the forearm horizontal, the arm length is measured from the acromion (or bony extremity of the shoulder girdle) to the olecranon (or tip of the elbow) with a plastic coated metric tape. The midpoint is marked on the dorsal surface. The participant should then relax the arm along the side of the body. The arm circumference is measured by drawing the tape snugly around the arm at the level of the midpoint marking. Care must be taken to keep the tape horizontal. Also, the tape should not indent the skin. The chart of arm circumference measurements and corresponding cuff sizes (shown below) is consulted, and the indicated cuff size is checked on the study form and used. (Note: If an arm measures 33.0, 33.0 will be entered for question 6a (Midpoint circumference of arm being used) on Form 110. For 6b (size of cuff), we would expect the center to use the Large Adult cuff, but if the patient's arm is short and chubby, the center could use the Adult cuff if that is the only cuff that will fit. (Try to use the same size cuff for every measure within a patient.) Do not use the cuff itself as a measurement device because the ranges marked on the cuff may not correspond with the table. A copy of this chart can be found on Form 110. This chart should be consulted for each arm measurement. The markings found on most blood pressure cuffs should not be used for reference because they may be incorrect.

Determination of Cuff Size Based on Arm Circumference

<u>Arm Circumference</u>	<u>Cuff Size (cm)</u>
< 24.0 cm	Child, Pediatric, Small Adult
24.0 to < 33.0 cm	Adult, Regular
33.0 to 41.0 cm	Large Adult
> 41.0 cm	Thigh, Extra Large

6.4.6 Application of the Blood Pressure Cuff

Next, the appropriate cuff (as determined in the arm measurement procedure) is placed around the upper right arm so that the midpoint of the length of the bladder lies over the brachial artery and the mid-height of the cuff is at heart level. The lower edge of the cuff, with its tubing connections, should be placed about 1 inch above the natural crease across the inner aspect of the elbow. The cuff is wrapped snugly about the arm, with the palm of the participant's hand turned upward. The wrapped cuff should be secured firmly by applying pressure to the locking fabric fastener over the area where it is applied to the cuff.

6.4.7 Determining the Peak Inflation Level

For each participant it is necessary to determine the pressure level to which the cuff is to be inflated for accurate measurement of the systolic pressure. This is because the pressure at the start of the reading should always exceed the systolic pressure, otherwise the first of the Korotkoff sounds will be missed (see Lecture #1). This starting pressure is called the Peak Inflation Pressure and is determined as follows. First, the cuff tubing should be attached to the Tycos Classic Hand Aneroid sphygmomanometer. While palpating the radial pulse, observe sphygmomanometer and inflate the cuff rapidly to 60 mmHg and then slowly inflate in increments of 10 mmHg until the pulse is no longer felt. If the pulse is still felt, the cuff pressure should be increased until the pulse disappears. Either the first or the second of these procedures will identify the Observed Pulse Obliteration Pressure. When this has been detected, the cuff is quickly and completely deflated. The Observed Pulse Obliteration Pressure is then added to 30 mmHg. This summed value is the Peak Inflation Level. The cuff is to be inflated to this level for all readings at this examination.

NOTE: All readings on the sphygmomanometer are made to the nearest even digit. Any reading that appears to fall exactly between markings on the column should be read to the next marking immediately above, i.e., 2, 4, 6, 8, or 0.

6.4.8 Pulse Measurement

Part of the blood pressure measurement procedure is the measurement of the pulse, as observed by palpation of the radial artery at the wrist. For simplicity, the right arm is to be used consistently for measurement of both pulse and blood pressure. This measurement serves two purposes: (1) to document the resting heart rate at the time of examination, and (2) to permit detection of gross irregularities of heart rhythm which may affect the interpretation of the blood pressure readings.

A good stopwatch should be used for the 5 minute waiting period prior to pulse measurement, 30 second pulse measurement, and 30 second intervals between blood pressure readings. The Cronus Stop Watch, Model 3-S, is an interval timer and is a preferred timing device. Of the various options, it seems to be the simplest and easiest to read and is generally available at a local sporting goods store. The address of the manufacturer is:

Cronus Precision Products, Inc.
2895 Northwestern Parkway
Santa Clara, California 95051

The measurement of pulse is performed only after the participant has been seated quietly, with feet flat on the floor, in an erect but comfortable posture, for at least five minutes. The patient should refrain from caffeine, smoking, and exercise at least one half hour prior to and until completion of blood pressure measurement. The elbow and forearm should rest comfortably on the table. With the palm of the hand turned upward, the radial pulse is palpated and counted for 30 seconds exactly. The number of beats in 30 seconds is recorded, multiplied by 2, and the product recorded as the heart rate. Any marked irregularity observed during this period should be called to the attention of the Principal Investigator and

the Blood Pressure Training Supervisor.

6.4.9 Blood Pressure Readings

Next, the observer should proceed to carry out the first blood pressure reading. Detailed instructions are given below for measuring blood pressure with a Tycos Classic Hand Aneroid sphygmomanometer.

6.4.10 Measuring Blood Pressure with a Tycos Classic Hand Aneroid Device

The steps for readings with the Tycos Classic Hand Aneroid device are described below.

- (1) Wait at least 30 seconds after complete deflation of the cuff following any preceding inflation.
- (2) Connect the cuff to the Tycos Classic Hand Aneroid device.
- (3) Place the ear pieces of the stethoscope into the ears, with the tips turned forward.
- (4) Apply the bell of the stethoscope over the brachial artery, just below but not touching the cuff or tubing. The brachial artery is usually found at the crease of the arm, slightly toward the body.
- (5) Using the previously determined peak inflation level, rapidly inflate to this level. The eyes of the observer should be focused on the dial of the aneroid sphygmomanometer. The observer should rapidly inflate the cuff.
- (6) By slightly adjusting the valve, deflate and maintain a constant rate of deflation at approximately 2 mm Hg per second, allow the cuff to deflate, listening throughout the entire range of deflation, from the maximum pressure past the systolic reading (the pressure where the first of two consecutive beats is heard), until 10 mm Hg below the level of the diastolic reading (that is, 10 mm Hg below the level where the last of two consecutive beats is heard).
- (7) Open the valve to deflate fully and disconnect the tubing. Remove the stethoscope earpieces from the ears.
- (8) Record the systolic and diastolic reading.
- (9) Repeat steps 3 through 9 two more times, waiting at least 30 seconds after complete deflation of the cuff following any preceding inflation. These are the Second and Third Tycos Classic Hand Aneroid Blood Pressure Values. Note: After the first and second readings, the patient's arm should be raised for 15 seconds. The arm is then lowered. Wait an additional 15 seconds. There is a total of 30 seconds between readings.
- (10) Ways to accentuate Korotkoff sounds: 1) While using the standard technique, rapidly inflate the cuff while the participant's arm is elevated, then, bring the participant's arm back to heart level and begin taking the reading. Or, 2) After the cuff is rapidly inflated to the Peak Inflation Level, have the participant rapidly open and close his or her fist six to eight times. Then, instruct the participant to relax their arm and begin taking the reading.

6.4.11 Criteria for Systolic and Diastolic Blood Pressure

To correctly identify the 1st-phase (systolic) and 5th-phase (diastolic) Korotkoff values, the observer must listen carefully via the stethoscope while reading and interpreting the aneroid dial. The systolic value can be identified as the pressure level where the first of 2 or more consecutive beats are heard in appropriate rhythm. The diastolic value can be identified as the pressure level where the last of two consecutive beats heard. The aneroid dial should be made to drop at 2 mm Hg per second, from the maximum pressure until 10 mm Hg below that of the last regular sound heard. The control of the deflation rate is essential for accurate readings and depends on handling of the bulb and its control valve.

PLEASE NOTE: A single sound heard in isolation (*i.e., not in rhythmic sequence*) before the first of the rhythmic sounds (systolic) or following the last of the rhythmic sounds (diastolic) does not alter the interpretation of the blood pressure.

6.4.12 Forgotten Blood Pressure Readings

If for any reason the observer is unable or has forgotten to complete any portion of the exam, and the participant is gone, leave the items blank on the paper form. If a blood pressure value is missed or forgotten, completely deflate the cuff and start over with a replacement reading after the proper interval. Do **not** re-inflate the blood pressure cuff during a reading. However, under no other circumstances may a replacement reading be obtained. Do **not** redo a reading that looks unusual to you.

6.4.13 Reporting the Blood Pressure Results to the Participant

The patient may wish to know his or her results before the form is entered into the database. If so, average the second and third Tycos Classic Hand Aneroid readings and give the results to the participant. State clearly the systolic and diastolic pressures and offer to write down these values for the participant.

6.5 Training Materials

6.5.1 Overview of Training Materials

Trainees are first oriented to the subject of blood pressure measurement with a series of lectures. A brief description of each is given here.

1. Blood Pressure Measurement - Problems and Solutions (lecture)

A general discussion of blood pressure, the history of its measurement, and some of the problems and solutions inherent in its measurement. (Section 6.5.4)

2. The Tycos Classic Hand Aneroid Device (lecture)

An explanation of the mechanics and the principles of the operation of this device and the importance of regular calibration checks. (Section 6.5.5)

3. Procedures in Blood Pressure Recording (lecture)

Step-by-step instructions on how to measure blood pressure using the Tycos Classic Hand Aneroid Sphygmomanometer. (Sections 6.5.7 - 6.5.16)

4. Local Blood Pressure Equipment Maintenance and Mercury Toxicity Safety Responsibility (notes).

For those using mercury manometers for calibration checks.

Step-by-step instructions on how to perform routine maintenance duties on both the Tycos Classic Hand Aneroid and conventional mercury sphygmomanometers (used for calibration checks every six months) (Section 6.5.16).

5. Training Observers in the Clinical Center (lecture)

Instructions for the Training Supervisor in local training. (Sections 6.5.21 - 6.6.3)

6.5.2 General Plan

When the supervisor feels that the trainee has reached a satisfactory level of proficiency in determining the systolic and diastolic blood pressure levels, the trainee should be given The Live Blood Pressure Reading Performance Evaluation (and two y-tube readings) (see Section 6.7.6). The observer must demonstrate to the training supervisor one or more complete and correct blood pressure determination procedures for 1) cuff selection by correct arm measurement, 2) determination of pulse, 3) determination of peak inflation level using the Tycos Classic Hand Aneroid, and 4) correct blood pressure measurement following the protocol. The Live Evaluation should be faxed to the DCC. The final tests to certify an observer will be a written test (provided by the DCC) and videotape test (provided by Shared Care) every 6 months. The test involves watching aneroid and mercury sphygmomanometer and listening to the simultaneous Korotkoff sounds during blood pressure measurements, then recording the systolic and diastolic levels for each on the videotape test sheet. The videotape test sheet is then faxed to Shared Care following the outlined instructions enclosed in the mailing from Shared Care.

6.5.3 Lecture Presentations

Five lectures are offered in this section to acquaint the trainee with the subject of blood pressure and its measurement.

The training of potential blood pressure observers should begin with a general discussion of blood pressure and some of the history of blood pressure measurement. The first lecture, "Blood Pressure Measurement - Problems and Solutions," addresses these 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 trainee 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 Tycos Classic Hand Aneroid Device," is accompanied by a demonstration that aids in the explanation of the mechanics and the proper use of this device and calibration check.

The third lecture is entitled, "Procedures in Blood Pressure Recording." This presentation gives instructions in the blood pressure measurement technique adopted by the HDFP, SHEP, and now AASK. Procedures for using both the conventional and the Tycos Classic Hand Aneroid devices are given.

6.5.4 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 that contribute to blood pressure regulation. Or, blood pressure can be described in terms of the striking excess in risk of death and disease that 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 observations is an informative summary of the specific sounds he described:

On the basis of his observations, 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, down 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 manometric 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 pass 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 observer 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 Rose⁷ distinguishes first random variation within each subject, and second, systematic variation which they subclassify as follows: "(i) alarmingly large differences in estimation between observers, sometimes as large as 15 mm Hg..., (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 - either the large arm cuff, or if necessary, the thigh cuff - 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 readings be taken in the sitting position, only after a minimum period of 5 minutes seated at rest, according to carefully prescribed procedures. As to differences between observers, a systematic difference as large as 15 mm Hg would indeed be alarming, and in fact unacceptable. However, a difference of ± 4 mm Hg is acceptable. In still another publication dealing with measurement of blood pressure, Rose presented in greater detail some components of the remaining major problem, observer 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 observers 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. For all the remaining problems, we have a single answer: TRAINING. We will talk shortly about the Tycos Classic Hand Aneroid 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 a lecture and a demonstration to acquaint you with the proper procedures for measuring blood pressure and also to familiarize you with the Tycos Classic Hand Aneroid device. Second, you will take actual live blood pressure readings. 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 training supervisor. 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 observer. 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 observers.

6.5.5 Lecture #2

The Tycos Classic Hand Aneroid device has achieved widespread acceptance in recent years, chiefly as an alternative to mercury devices and their associated disadvantages. An inherent drawback to aneroid devices is the fact they must be checked for calibration at regular intervals (every 6 months) and adjusted if necessary. The mercury manometers are still considered the gold standard in blood pressure measurement. Bi-annual (every 6 months) calibration checks for the Tycos Classic Hand Aneroid must be done. If centers are unable to use mercury sphygmomanometers for calibration at their center, you can send your Tycos Classic Hand Aneroid Device to Welch Allyn Medical Division, Jeanne Charleston at Johns Hopkins or Beth Wilkening at Emory University for calibration as described in Section 6.5.16 of this chapter.

6.5.6. Lecture #3

Procedures In Blood Pressure Recording

These procedures for 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 of criteria for measurement, we specify methods for the entire sequence of steps in blood pressure recording. For all observers, 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 Tycos Classic Hand Aneroid.

6.5.7 Equipment and Supplies

1. The equipment needed by each observer includes a Tycos Classic Hand Aneroid sphygmomanometer in good condition,
2. Access is needed to the full set of Welch Allyn V-Lok 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 observer.
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.
7. A plastic coated measuring tape in metric units is required for determination of the correct cuff size for each participant.
 8. A ballpoint 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.
 - A Mayo stand (or other similar device) should be available for use in measuring standing blood pressures.
 10. The appropriate study form must be in place before measurement begins.

6.5.8 Arm Measurement

11. Measurement of the arm is required for selection of the proper cuff. For this measurement, the arm should be bare.
12. The measurements are taken on the right arm, with the participant standing, holding the forearm horizontal.
13. Arm length is measured from the acromion or bony extremity of the shoulder girdle,
14. to the olecranon, or tip of the elbow.
15. The full arm length from acromion to olecranon is measured, and
16. the midpoint is marked on the dorsal surface of the arm.
17. 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.
18. The chart of arm circumference measurements and corresponding cuff sizes is consulted, and
19. the proper cuff size is checked. Indicate this cuff size on the form. (Note: If an arm measures 33.0, 33.0 will be entered for question 6a (Midpoint circumference of arm being used) on Form 110. For 6b (size of cuff), we would expect the center to use the Large Adult cuff, but if the patient's arm is short and chubby, the center could use the Adult cuff if that is the only cuff that will fit. (Try to use the same size cuff for every measure within a patient.))

6.5.9 Preparation for Actual Readings

20. The participant 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 is to be applied must be bare.
21. The brachial artery is located by palpation and marked,
22. as is the midpoint of the rubber bladder within the cuff. Often this point is marked on the cuff itself.
23. 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.

24. The Tycos Classic Hand Aneroid sphygmomanometer is then connected with the cuff.
25. The manometer is positioned so that the observer's can read the dial without a glare.
26. The radial pulse is located, and
27. While palpating the radial pulse, observe the dial of the aneroid sphygmomanometer and quickly inflate to 60 mmHg and then slowly inflate in increments of 10 mmHg until the pulse is no longer felt. If the pulse is still detected, the cuff is inflated slowly by increments of 10 mmHg until the pulse disappears. Either the first or the second of these procedures identifies the Observed Pulse Obliteration Pressure.
28. The cuff is quickly and completely deflated.
29. The observed value and 30 mmHg are used to calculate (by addition) the Corrected Pulse Obliteration Pressure. Both are recorded on the form.
30. The sum of the two equals the Peak Inflation Level (PIL)

6.5.10 Pulse

31. After the period of 5 minutes at rest has been completed, the radial pulse is counted for a timed interval of exactly 30 seconds.
32. The 30-second count is multiplied by 2 and recorded to give the full number of beats per minute.

6.5.11 First Blood Pressure Reading

33. To perform the measurement of blood pressure itself, the brachial artery is again palpated. Note that the arm remains bare.
34. The stethoscope earpieces are put in place with the earpieces positioned forward, and
35. 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.
36. The cuff is quickly inflated to the Peak Inflation Level.
37. The cuff is then deflated very steadily at 2 mmHg per second, to a level 10 mmHg lower than the level of the last Korotkoff sound heard.
38. The manometer level is now dropped quickly to the zero level for this reading.
39. The cuff is then disconnected and the stethoscope removed.
40. The observed values for the SBP, DBP, are recorded.

6.5.12 Between Readings

41. If the cuff is uncomfortable for the participant you may remove it, and
42. the observer will raise the participant's arm overhead for 15 seconds without the participant's assistance.
43. The arm is then lowered gently for an additional 15 seconds. There is a total

of 30 seconds between readings.

44. If the cuff was removed it should be replaced, and
45. the Tycos Classic Hand Aneroid sphygmomanometer is reconnected.

6.5.13 Second Blood Pressure Reading

46. The second reading is carried out exactly as the first on the Tycos Classic Hand Aneroid.
47. The observed SBP, DBP, are recorded,

6.5.14 Between Readings/Third Blood Pressure Reading

- The cuff may be removed once again and the entire sequence is repeated from having the observer raise the participant's arm overhead for 15 seconds, lowering the arm and waiting an additional 15 seconds before taking the third Blood Pressure Reading.
Note: There is a total of 30 seconds between blood pressure readings.
- As before, the observed SBP, DBP, are recorded.
- The second and third readings are averaged to get the average systolic and diastolic for the visit.

6.5.15 Standing Blood Pressure Readings

After completing these sitting blood pressure readings, the adjusted arm support (Mayo stand, or a patient bedside adjustable tray holder) should be situated at the participant's immediate right so that unnecessary movement or walking will not occur when the participant is asked to stand.

The participant is asked to stand quietly for 2 minutes. After the 2 minutes, the observer should raise the participant's arm for 15 seconds. The arm is then placed on the Mayo stand. Immediately, the pulse should be taken for 30 seconds and multiplied by 2 to give the full number of beats per minute. The time lapse from standing is now two minutes and forty-five seconds and the cuff is inflated for standing blood pressure. The cuff is inflated to the peak inflation level. (Note: If the systolic measurement is heard right away, deflate the cuff and recalculate the Peak Inflation Level for the patient.) The pressure is deflated at 2 mmHg. It is deflated at 2 mmHg per second until 10 mmHg below the last Korotkoff sound heard and then deflated quickly and completely. Record your results. The arm is lowered to the side for 15 seconds. During the 15 seconds that the arm is at the participant's side, the observed SBP, DBP values are recorded.

The cuff is removed. The participant is then asked to be seated SBP and DBP are recorded on the form.

6.5.16 Calibration of the Tycos Classic Hand Aneroid

Calibration checks are done every six months. Record calibration checkpoints on the Blood Pressure Aneroid Calibration Form 109. You will need the following equipment:

- Mercury sphygmomanometer
 - “Y” connector
 - Inflation bulb and valve attached
1. Connect one tube to the mercury manometer.
 2. Connect the Tyco’s aneroid dial to the other tube.
 3. Cuffs and bags are not used when conducting calibration checks.
 4. Slowly inflate the instruments to 250 mmHg and compare the readings.
 5. They should be the same, however a deviation of t/- 4mmhg is acceptable.
 6. Record the readings you obtain.
 7. Repeat the procedure at 160 mmHg.
 8. Repeat at 70 mmHg.

Repeat this procedure again at each level (250, 160 and 70 mmHg). If, when averaged, there is a deviation of greater than t/-4mmHg at any level, the aneroid device being tested is inaccurate and needs to be sent back to Welch Allyn for repair. Call Welch Allyn prior to sending the device. Welch Allyn will give the clinical center an order number that the center will need to reference.

Note: Remember, the mere fact that the needle points to zero on the dial of the aneroid manometer when the compression is deflated does not necessarily mean that the instrument is accurate over the entire pressure range. “Primer Of Clinical Blood Pressure Measurement by George E. Burch,M.D. and Nicholas D. Pasquals, M.D.

“The readings on the dial at different pressures should check with those of a properly constructed and functioning mercury manometer. The fact that the pointer indicates zero may be no guarantee of accuracy over the whole pressure range”. American Heart Association, “Recommendations for Human Blood Pressure Determinations by Sphygmomanometers”.

If AASK Clinics cannot perform biannual calibration checks, the center should send their equipment to one of the following sites:

Welch Allyn Medical Div
 95 Old Shouls Road
 Arden, NC 28704
 Telephone: 1-800-535-6663

Emory University
 Hypertension Research Center
 C/O Beth Wilkening, P.A.
 125 Clairemont Avenue, Suite 410
 Decatur, GA 30030
 Telephone: 404-370-7340

Johns Hopkins ProHealth
 C/O Jeanne Charleston
 1849 Gwynn Oak Ave, Suite 1
 Baltimore, MD 21207
 Telephone: 410-281-1600

6.5.17 Local Blood Pressure Equipment Maintenance and Mercury Toxicity Safety Responsibility (Only for clinics using mercury manometers for calibration checks)

The condition of the instruments for blood pressure measurement is too often ignored in common practice and should be a special responsibility of the blood pressure observer. This person should be acquainted with mercury toxicity safety procedures as well as construction and function of all the blood pressure equipment. The cuffs and stethoscope, cleanliness and general working order can usually be determined by simple inspection. For the conventional mercury sphygmomanometer, handling of breakable parts and of mercury and oxidized waste requires more careful attention.

6.5.18 Inspection of the Tycos Classic Hand Aneroid Manometer

Unless obviously damaged due to dropping or other accident, the Tycos Classic Hand Aneroid sphygmomanometer is expected to operate without disturbance of its measurement performance. Bi-annual calibration checking must be done to ensure against undetectable accuracy problems.

6.5.19 Training Observers In The Clinical Center

There are three distinct sections involved in the responsibility of the local Training Supervisors. 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 Data Coordinating Center.

6.5.20 Preparation for Training Observers

- A. Gather all the blood pressure equipment.
 - 1. Both the conventional and Tycos Classic Hand Aneroid manometers
 - 2. All four basic sizes of blood pressure cuffs with bulbs
 - 3. A bell stethoscope

Familiarize yourself with all the blood pressure equipment. Prepare for mercury safety (for clinics using mercury for calibration checks) procedures and prepare an equipment maintenance schedule.

- B. Gather all training materials.
 - 1. This training manual
 - 2. The appropriate forms and paper
 - 3. Videotape machine
 - 4. Black ball-point pen

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 trainees. Be sure you have plenty of photocopies of all the forms (the Written Examination, the Live Blood Pressure Performance Evaluation Sheet (see Section 6.7.6), and the Videotape Test Sheet (provided by Shared Care)).

6.5.21 Training Tips

- A. Schedule the training sessions. An unhurried schedule gives the trainee 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.
- B. 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.
- C. The certification of the trainee and duties as an observer should not be planned for the same day. The trainee cannot complete the certification and begin taking participant blood pressures that same day. Plan time to allow for the return of the documentation to Shared Care and to the Data Coordinating Center. Confirmation of certification will be made by telephone to the Blood Pressure Supervisor once all materials have been received. The Videotape Test should be faxed to Shared Care for scoring. The Shared Care confirmation showing all blood pressure measurers have successfully completed the video tape test should be faxed to the DCC along with the Live Evaluation and written test.

6.5.22 Documentation of Certification

- A. Each person in the Clinical Center that will be filling out any part of a blood pressure form will need certification ID. This includes the blood pressure observers.
- B. The Written Examination should be taken by the trainee and faxed to the DCC.
- C. The Live Blood Pressure Reading Performance Evaluation and two y-tube readings should be carefully followed to ascertain that the trainee has a clear understanding of the procedures. This evaluation should be completed by the supervisor as a passive observer. Avoid prompting the trainee. The trainee 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 faxed to the DCC.
- D. The practice videotape should be employed to familiarize the trainee with the process of the videotape. Do not overexpose the trainee to the actual videotape test. The test should be faxed to Shared Care following the outline of instructions enclosed in the mailing from Shared Care. If a systematic problem is discovered, Shared Care will instruct you as to the type of problem discovered. The specific problem should not be identified to the trainee, as this may artificially bias the trainee'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 the trainee would need to be excluded from taking blood pressures. The Data Coordinating Center will need to have complete documentation of the certification before the trainee can be employed as a blood pressure observer. We suggest the supervisor keep the originals and send photocopies to the Coordinating Center. The Coordinating Center will instruct the Training Supervisor when recertifications should be scheduled, every six months.

6.6 Certification Procedures And Criteria

6.6.1 Three Steps Needed For Certification

In order to standardize the previously described methods of blood pressure measurement and to ensure that a high level of performance is attained, a three-part training session has been developed. After successful completion, an observer is certified to take blood pressures in the study program. The three steps needed for certification are enumerated below.

1. The first step of blood pressure training is the completion of the Written Examination after lectures 1 - 3 have been presented. This is a short examination consisting of questions that test the blood pressure observer's knowledge and understanding of the measurement technique detailed in the training course.
2. The second step is the successful completion of The Live Blood Pressure Reading Performance Evaluation and two y-tube readings. The training supervisor is to verify the correct procedure for blood pressure measurement by observing the trainee in one or more complete and uninterrupted exercises of the full procedure. When carried out without procedural errors, this record should be completed, signed and faxed to the DCC. Errors of procedure should be reviewed, discussed and corrected, until one completed determination is accomplished without error.
3. The third step is a series of blood pressure readings presented on a videotape to test the observer's identification of the systolic and diastolic Korotkoff sounds. This tape mimics the actual blood pressure measurement setting by providing a series of blood pressure readings which consist of both aneroid and mercury sphygmomanometers and the audible Korotkoff sounds. An observer is certified if the criteria of the scoring procedure are successfully met. The criteria for the scoring procedure are not available to the Clinical Center or to the observers. The scoring will be done at Shared Care upon receipt of the observer's test sheet.

As a means of maintaining a high level of quality and standardization over time, blood pressure observers will be recertified in the videotape, written test and live evaluation every six months. Re-certification will involve, repeated testing by viewing the videotape and submitting a completed test sheet, as well as live measurement performance evaluation and a written test. The Data Coordinating Center will notify the Clinical Centers as to the schedule and requirements of the recertification. A further description is in Section 6.7.2.

6.6.2 Instructions for Taking the Video Test

Viewing of the videotapes, "Blood Pressure Standardized Test. Measuring Blood Pressure. Aneroid Examples" may be done in a group or individually. The videotape consists of practice readings followed by twelve systolic and diastolic sequences. After each sequence, the observer should record, on the recording sheet provided, the systolic and diastolic reading for that sequence. All entries should be completely legible and written in black ink. Leading 0's should be entered if appropriate. The manometer in the videotape is read exactly as one would be read in actual practice. Each blood pressure should be read to the nearest even digit. The videotape also includes a blood pressure with an auscultatory gap.

6.6.3 Three Study Forms Required For Certification Procedures

The three study forms required for certification every six months include:

1. The Written Examination;
2. The Evaluation Sheet for The Live Blood Pressure Reading Performance Evaluation;
and
3. The Videotape Test Sheet.

6.7 Blood Pressure Measurement Quality Control

6.7.1 Overview

There are two primary methods for monitoring the performance of trained observers in the measurement of blood pressures during the course of an observational study. The first is the completion of an Annual Recertification set of procedures. The second is the three times per year monitoring by the Data Coordinating Center of all observers for digit preference.

In addition to these, AASK Cohort 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 every six months.
3. Retraining of observers having difficulties with standardized measurements.
4. Quarterly (four times per year as specified by the DCC) observations by the Training Supervisors of data collection techniques of the Blood Pressure Observers on either a patient or AASK personnel, using the "Live Blood Pressure Reading Performance Evaluation" checklist at the end of this chapter. One checklist is used for each blood pressure observer. The original should be kept on file and will be reviewed at site visits.
5. Quarterly (four times per year as specified by the DCC) simultaneous Y-Tube observations of each Observer by the blood pressure Training Supervisor on either a patient or AASK personnel (described in Section 6.7.4).
6. Frequent staff meetings to provide feedback.
7. Continuous editing and analysis of data by the Data Coordinating Center.
8. Presentation of data analyses to the Clinical Centers by the Data Coordinating Center to provide feedback three times per year.
9. Equipment maintenance program.
10. Documentation of the "Live Blood Pressure Reading Performance Evaluation" Checklist, Y-tube stethoscope observations, and weekly inspections will be sent to the DCC. The dates of the Tycos Classic Hand Aneroid Sphygmomanometer biannual calibration checks will be entered on Form 109.

6.7.2 Annual Recertification and Retraining

As with the initial certification process this recertification process (every six months) includes the successful completion of:

- * a written test
- * a live evaluation
- * a videotape test.

It is recommended that Training Supervisors demonstrate the live evaluation centrally each year. Recertifications for the other Blood Pressure Observers will also be every six months.

The recertification procedures for the Blood Pressure Observers will be conducted at the Clinical Centers. However, scoring of the video tests will be done by Shared Care. The Live Evaluation and written test should be faxed to the DCC. The confirmation from Shared Care showing all staff measuring blood pressure have successfully completed the videotape test should also be faxed to the DCC. The DCC is responsible for identifying who is a certified blood pressure observer. A report based upon the results of these tests may be presented to the Steering Committee and the Policy Board. This report would describe how well the observers are measuring blood pressure levels under standardized conditions, and how many observers had difficulty being recertified.

Of course, the results of the tests may indicate that an observer may need to be retrained in some or all aspects of blood pressure measurement. If this is required, this person will discontinue the measurement of blood pressure levels for the trial until he or she is successfully recertified by the Coordinating Center. Central retraining may be required.

Also, if an observer misses a recertification cycle, he or she must repeat the training program.

6.7.3 Monitoring for Digit Preference

It is well documented in other large blood pressure studies that even well trained observers 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 a "8", rather than the actual value. For example, an observer with a "0" digit preference may record an 82 mm Hg DPB (or a 78 mm Hg) as 80 mm Hg.

NO OBSERVER SHOULD EVER HAVE A DIGIT PREFERENCE.

The recertification process should dampen, on an annual basis, any incipient digit preference, but three times per year monitoring and presentation of actual blood pressure measurements by the Data Coordinating Center will identify problems more immediately. If a problem is identified, the blood pressure consultant to the AASK Cohort (or his designee) will be notified and corrective procedures implemented. Possible re-training and recertification may be necessary before the regularly scheduled certification.

6.7.4 Y-Tube Stethoscope Observations

Y-Tube stethoscope observations are done for quality control purposes. The Training Supervisor has each Observer go through the entire blood pressure measurement procedure using "Live Blood Pressure Reading Performance Evaluation" checklist. Each center must have at least one other staff member certified. The Observer and Supervisor listen with the Y-tube and record the values on separate sheets. Two measurements on one subject are obtained and will be kept on file and reviewed at site visits.

It should be emphasized again that some difference between supervisor and trainee is to be expected (a difference of ± 4 mm Hg is allowed), and that exact correspondence should not be expected nor taken even implicitly as a criterion of accurate performance by the trainee. 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 Supervisor's close involvement with the Blood Pressure Observer. Any problems identified by the Supervisor or raised by the Observer should be discussed and, as far as possible, resolved.

6.7.5 Responsibilities of the Data Coordinating Center and The Training Supervisors

It is the responsibility of the Data Coordinating Center and Shared Care to train and certify the Training Supervisors. **It is primarily the responsibility of the Training Supervisors to train at least one other observer.** However, only the Data Coordinating Center is able to certify an observer, as described above.

If, between recertifications, the Data Coordinating Center and/or a Training Supervisor have evidence that an observer is not performing well, the three parties will meet to discuss the matter. It may be necessary for the Data Coordinating Center to temporarily rescind a certification and retrain the observer. In this case, until the observer is recertified, he or she may not take blood pressure measurements for AASK.

It is also the responsibility of the Data Coordinating Center to monitor the specific activities of the Training Supervisors. In addition to the continuous monitoring of all incoming blood pressure data (e.g., for digit preference or bad values), the files of the "Live Blood Pressure Reading Performance Evaluation" checklists and Y-tube observations which should be done quarterly and should be faxed to the DCC and will be reviewed at each site visit for completeness and accuracy. Also at these site visits, the Training Supervisors themselves will undergo checklist monitoring and Y-tube observation. Finally, the Training Supervisors themselves will be recertified every six months.

6.7.6 **LIVE BLOOD PRESSURE READING PERFORMANCE EVALUATION**
(Used for Certification/Recertification and for Quality Control)

The original should be kept on file at the Clinical Center and a copy should be sent to the DCC.

Trainee's Name: _____

Date: __ __/__ __/__ __ __ __

Center: _____

A. **Equipment and Supplies**

The trainee should indicate that all equipment and supplies needed for blood pressure measurements are present. Check each item as identified:

- _____ (1) Tycos Classic Hand Aneroid Sphygmomanometer
- _____ (2) Welch Allyn V-Lok Cuffs - full set of 4 ("child" or "pediatric," "adult" or "regular," "large adult," and "thigh")
- _____ (3) Inflation Bulb
- _____ (4) Bell stethoscope
- _____ (5) Mayo stand or bedside table
- _____ (6) Watch with second hand or digital second display
- _____ (7) Measuring tape
- _____ (8) Black ball point pen
- _____ (9) Study Form 110

B. **Arm Measurements**

The following steps are properly carried out:

- _____ (1) Subject standing
- _____ (2) Arm bare from elbow to shoulder
- _____ (3) Arm at 90 degree angle
- _____ (4) Arm length measured from the acromion to the tip of the elbow
- _____ (5) Midpoint of arm marked at dorsal aspect
- _____ (6) Arm relaxed at side
- _____ (7) Circumference measured with tape horizontal
- _____ (8) No indentation of skin
- _____ (9) Mark at midpoint of arm
- _____ (10) Value checked with chart to ascertain proper cuff size
- _____ (11) Proper cuff size checked on study form (Form 110)

C. Preparation for BP Readings

- _____ (1) Brachial artery palpated
- _____ (2) Midpoint of bladder within the cuff located
- _____ (3) Cuff applied with midpoint of bladder over brachial artery
- _____ (4) Arm positioned with midpoint of cuff width at "heart" level; lower edge 2 to 3 cm (1 inch) above crease
- _____ (5) Tycos Classic Hand Aneroid sphygmomanometer connected to cuff
- _____ (6) sphygmomanometer scale (midpoint) is at eye level
- _____ (7) radial pulse located
- _____ (8) cuff is inflated quickly to 60 mm Hg
- _____ (9) cuff is further inflated slowly by increments of 10 mm Hg (if pulse present at 60 mm Hg) until the pulse is no longer felt.
- _____ (10) cuff is quickly and completely deflated
- _____ (11) Observed Pulse Obliteration value is correctly recorded on the form
- _____ (12) the Correct Pulse Obliteration Pressure + 30 are added to get the Peak Inflation Level

D. Measurement of Pulse

- _____ (1) Five-minute period at rest is completed
- _____ (2) Radial artery palpated
- _____ (3) Counting with watch, full 30 seconds
- _____ (4) Recording of 30-second count and correct doubling

E. Measurement of Blood Pressure

- _____ (1) Brachial artery palpated
- _____ (2) Stethoscope in ears
- _____ (3) Bell over artery, without cuff or tubing contact
- _____ (4) Cuff inflated quickly and smoothly to the Peak Inflation Level
- _____ (5) Deflation at 2 mm Hg/second to 10 mm Hg below K5
- _____ (6) Cuff quickly and completely deflated
- _____ (7) Cuff disconnected
- _____ (8) Recording of SBP and DBP values

F. Between Readings

- _____ (1) Cuff removed or tubing disconnected if uncomfortable
- _____ (2) Arm raised passively overhead for 15 seconds. (Make sure the patient is not supporting the arm at all)
- _____ (3) Arm lowered and cuff replaced with attention to brachial artery and midpoint of bladder; lower edge 2 to 3 cm (1 inch) above crease of the elbow. Note: There is a total of 30 seconds between readings.
- _____ (4) Cuff reconnected

G. Second Seated Blood Pressure Reading

_____ (1) Conforms with procedures as in E and F above

H. Third Seated Blood Pressure Reading

_____ (1) Conforms with procedures as in E above

I. Standing Blood Pressure Measurement

- _____ (1) After completing these sitting BP readings, the Mayo stand should already be situated at the participant's immediate right side
- _____ (2) Ask the participant to stand quietly for 2 minutes (Arm should be at the patient's side)
- _____ (3) Arm raised passively overhead for 15 seconds (Make sure the patient is not supporting the arm at all)
- _____ (4) Arm is then placed on the Mayo stand or bedside table
- _____ (5) Radial artery palpated
- _____ (6) Counting with watch, full 30 seconds
- _____ (7) Recording of 30-second count and correct doubling
- _____ (8) Cuff inflated quickly and smoothly to the Peak Inflation Level
- _____ (9) Deflation at 2 mm Hg/second to 10 mm Hg below K5
- _____ (10) Cuff quickly and completely deflated
- _____ (11) Cuff disconnected
- _____ (12) Recording of SBP and DBP values
- _____ (13) Patient's arm is lowered to side
- _____ (14) Cuff is removed
- _____ (15) Any unfinished calculations can be completed

J. Completion

- _____ (1) Q200 and Q201 completed on Form 110
- _____ (2) Closure of Tycos Classic Hand Aneroid manometer case for storage

I certify that all steps were followed correctly and according to the AASK Cohort Protocol.

BP Supervisor Signature or BP Observer Signature (if certifying Supervisor)

Remarks: _____

This Section is for QC purposes only:

Y-tube Stethoscope Observations: ___/___ Initials ___

___/___

___/___ Initials ___

___/___

Dates that the Tyco Classic Hand Aneroid Sphygmomanometer was inspected (insert dates here or send a copy of your log).

6.8 Acknowledgment of Adaption

AASK Cohort
Blood Pressure Measurement
Training and Quality Control
Adapted By
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Karen Brittain
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Adapted from the Procedures
of the Systolic Hypertension in the Elderly Program (SHEP)
January 1985

by Darwin R. Labarthe and Melanie Palmer

which were
Based on the Procedures
of the Hypertension Detection and Follow-up Program (HDFP)

by
Darwin R. Labarthe, M.D., Ph.D.
Sharon B. Poizner-Cooper, Ph.D.
Gary R. Cutter, Ph.D.
Barbara H. Casey, B.A.

Some text adapted from the ARIC Protocol 11:
"Sitting Blood Pressure and Postural Changes" (4/16/87)

6.9 References

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AASK Cohort
BLOOD PRESSURE MEASUREMENT
TRAINING AND QUALITY CONTROL

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CHAPTER 7. CLINICAL CENTER PROCESSING AND SHIPPING OF SAMPLES FOR THE GENETICS CORE LABORATORY

7.1 Genetic Consent/ IRB Approval

After IRB approval is obtained at each AASK site, patients will be asked to participate in the proposed genetic studies. Each center will need to send a copy of the IRB approval letter to Dr. Lipkowitz at the Genetics Core Center and a copy of the stamped consent form to Coriell Institute for Medical Research.

7.2 Collection

After consent is obtained, blood (20 ml) will be drawn into ACD (yellow top) tubes whose tops have been wiped with alcohol swabs and allowed to air dry. Dr. Lipkowitz at the Genetics Core Center has provided the tubes to each site.

7.3 Labeling

Tubes will be labeled with the AASK patient ID number and name code and the date the sample was drawn. No other identifiers should be placed on the tubes. If wrapping the label around the tube, affix the label towards the bottom so that the volume of blood collected can be measured and make sure none of the identifying information is blocked.

7.4 Storing

After blood is drawn, it should be kept at room temperature until shipped. **Never heat, refrigerate or freeze blood samples!!!**

7.5 Shipping Instructions

Samples will be sealed in approved leakproof, padded containers. Do not pack more than 8 tubes per mailer. Ship to Coriell Institute for next morning delivery using the Federal Express labels and shipping containers provided by Dr. Lipkowitz at the Genetics Core Center. A copy of the appropriate genetics mailing form (Form 120 or Form 121) should be included in the shipment for each sample that is sent.

Blood should be shipped the day it is drawn if there are 3 or more patients' samples that day or no samples to be obtained/no patients scheduled the next day.

If there are less than 3 patients' samples:

Monday and Tuesday samples can be batched and shipped Tuesday.

Tuesday and Wednesday samples can be batched and shipped Wednesday.

Wednesday samples cannot be held over and must be shipped Wednesday.

Thursday bloods should always be shipped Thursday.

Friday bloods should be shipped Friday for Monday morning delivery.

Genetics blood samples will be sent to:

AASK Study
Coriell Cell Repositories
Coriell Institute for Medical Research
403 Haddon Avenue
Camden, NJ 08103

The telephone number for Fed Ex is 1-800-463-3339.

After samples are sent, sites should email Cynthia Royds (croyds@cimr.umdnj.edu) at Coriell with the Fedex tracking number of the samples. Also, let her know the number of cases and/or tubes being shipped. She will then track the samples and send back a reply that sent samples are received.

Cynthia Royds
Data Manager
Coriell Institute for Medical Research
403 Haddon Ave.
Camden, NJ 08103

Phone: 856-757-9756

FAX: 856-757-9737

E-mail: croyds@cimr.umdnj.edu

7.6 Reports

Coriell will report on a weekly basis to the DCC. This report will consist of the samples received and processed successfully.

The Genetic Core Center at Mount Sinai will report on the number of samples from which DNA is extracted as DNA extractions are performed.

CHAPTER 8. SPECIMEN PROCESSING AND STORAGE AT THE GENETICS CORE LABORATORY

8.1 ACD Tubes

At Coriell, one ACD tube of blood will be employed for controlled freezing of purified PBMC (see section 8.5). The second tube will be refrigerated and mailed to Dr. Lipkowitz at Mount Sinai for DNA processing (sections 8.2-8.3). Frozen PBMC will be stored at Coriell until needed for immortalization as described in Section 8.4.

8.2 Splitting on Receipt of Samples

When received, blood will be divided into 3 aliquots: 10 ml will be used to isolate genomic DNA; 10 ml will be used either to immortalize lymphocytes or for controlled freezing of 4 aliquots of purified PBMC; approximately 50 ul will be spotted onto IsoCode Stix (Schleicher&Schuell) and dried as an archive for future DNA isolation/sample identification/quality control.

8.3 DNA Extraction

Ten ml of blood will be processed immediately for DNA. Genomic DNA will be extracted from peripheral blood leukocytes using the Puregene kit (Gentra Systems, Minneapolis, MN). DNA concentration will be calculated from absorbance at 260 nm measured by a UV/VIS spectrophotometer. Purity will be estimated by the ratio of absorbance at 260nm/280 nm, and confirmed by agarose gel electrophoresis.

8.4 Immortalization of Leukocytes with Epstein-Barr Virus

Ten ml of blood will be used to transform leukocytes as a renewable permanent repository of study patient DNA. Blood will be diluted with an equal volume of RPMI 1640, layered over Ficoll-Paque (5 ml blood-RPMI/3 ml Ficoll-Paque) and centrifuged at 400 x g for 30 min. The lymphocyte layer will be removed and washed twice with RPMI. Lymphocytes (4×10^6) will be added to 4 ml of transformation cocktail containing 40% Epstein-Barr virus supernatant from 10 da cultures of B95-8 marmoset cells (ATCC)/60% RPMI with HEPES, 15% FCS, and 1 ug/ml cyclosporine A. Cells will be placed in a T25 flask; at 7 da cells will be refed with cocktail by replacing 1 ml of the medium. Beginning at 14 days, cells will be fed twice weekly by replacing the medium with RPMI complete/20% FCS. When cells begin to expand, culture volume will be increased to maintain exponential growth. At 3-6 weeks, when cells are immortalized, aliquots will be frozen for storage in liquid nitrogen, and DNA harvested for candidate gene and MALD studies. To date, immortalization has been successful at a 90-95% rate. DNA from immortalized cells has been tested by PCR of exons of the human UAT, products sequenced, and sequences compared to PCR products of DNA from blood; results were identical.

8.5 Controlled Freezing of Purified PBMC

Because of the significant resources (technician time and cell culture incubator space) required for immortalization of cells, at times it will be necessary to cryopreserve lymphocytes for future immortalization as described by Beck et al [1]. This procedure in fact is likely to yield increased success at immortalization since there is approximately a 90% success rate/aliquot. In brief, blood will be diluted with an equal volume of RPMI/HEPES and lymphocytes separated on a Histopaque-1077 gradient. The lymphocyte layer will be washed twice in the same medium, and the final pellet will be resuspended in RPMI/HEPES, 30% heat inactivated FBS, 6% DMSO, divided into 4 aliquots ($2-8 \times 10^6$ cells/aliquot), and frozen at a controlled rate to -80° C.

8.6 Tests to be Done

Dr. Lipkowitz reports:

We are not doing genetic "testing" per se as this is not a clinical test nor are we sharing results with subjects as this would involve amongst other things counseling.

We will be looking at a large number of potential candidate genes for renal disease, hypertension, and cardiovascular disease as well as at genes that may affect the effectiveness of particular medications. We are also asking subjects for permission to share cells and DNA with other groups performing similar studies as well as for potential studies that future AASK data may suggest. In addition, we will perform studies to identify new genes for these disorders, and share DNA with other groups doing similar studies.

If this is not enough, we can arrange to get summaries of ongoing Ancillary Studies or the IRBs that need them.

8.7 References

Beck, J.C., *et al.*, *Successful transformation of cryopreserved lymphocytes: a resource for Epidemiological studies*. *Cancer Epidemiol Biomarkers Prev*, 2001. 10(5): p. 551-4

CHAPTER 9. CLINICAL CENTER SAMPLE COLLECTION AND HANDLING

9.1 Laboratory Responsibilities

- A. The clinical center AASK technician will be responsible for collecting all samples, processing them and mailing them to the Central Biochemistry Lab (CBL) or sending them to the appropriate clinical center lab.
- B. The clinical center local laboratories will perform all of the testing and reporting of results for the CBC.
- C. The Central Biochemistry Laboratory at the Cleveland Clinic Foundation will receive and perform all testing and reporting of results for the routine chemistry, including calcium & phosphorus, lipid profile, insulin and 24-hour urine as indicated in [Table 3 and Table 4] of the Protocol.

Table 9.1 Central Biochemistry and Local Labs – Non ESRD Patients

VISIT	10ML RED TOP OR 9.5ML SST (RED/GRAY SPECKLED TOP) (Form 122)	10ML LAVENDER TOP (EDTA) FOR INFLAMMATORY MARKERS AND/OR FROZEN PLASMA (At C0-Captured on F122) (C12, 24, ect., Captured on Form 127)	LAVENDER TOP (EDTA) FOR LOCAL LAB CBC (Form 113)	24-Hour Urine (Form 123)
C0	2	1	1	25 mL
“C0.1”	2			
C6	2			
C12	2	1	1	25 mL
C18	2			
C24, etc	2	1	1	25 mL

9.2 Telephone/Written Communications

- A. Telephone inquiries having to do with aspects of sample collection/processing/ mailing may be directed to the Central Biochemistry Laboratory. Calls to the Central Biochemistry Laboratory will be answered between 9:30 a.m. and 6:00 p.m. Eastern time, weekdays only.

- B. Written inquiries can be forwarded to the Central Biochemistry Laboratory via the FAX number, 216-444-7004.
- C. The Central Biochemistry Lab will communicate with participating clinical centers over electronic mail, fax, or at the addresses/phone numbers listed in the AASK Address Directory.

9.3 Central Biochemistry Laboratory

9.3.1 Procurement of Mailing Supplies for Biochemistry Samples

The Central Biochemistry Laboratory will provide all necessary mailing supplies to the clinical centers for mailing of Biochemistry samples. This includes styrofoam insulated mailing containers with cardboard outer mailing boxes, 30 ml polypropylene urine mailing tubes, 10 and 5 mL serum and plasma mailing tubes, tube labels, zip-lock plastic bags, packing tape, and suitable mailing labels.

Participating clinical centers will be expected to provide sample processing supplies (e.g., vacutainer tubes, needles and other phlebotomy supplies).

9.3.2 Distribution of Mailing Supplies to Participating Clinical Centers

Mailing supplies will be shipped to each participating clinical center, as needed. Styrofoam mailing containers will be reused whenever possible and replaced by the Central Biochemistry Lab as needed. Plastic sample mailing tubes and zip-lock bags are discarded by the Central Biochemistry Lab after each mailing and replaced. Requested supplies will be sent back to clinical centers with each remailing of shipping boxes.

9.3.3 Postal/Overnight Courier Inquiries

Participating clinical centers should keep a log of sample mailing dates for reference. The Central Biochemistry Lab will log-in samples received. In the event that mailing difficulties occur, the Central Biochemistry Lab will follow-up as needed when notified of a problem.

9.3.4 Sample Package Receipt at CCF

Samples will arrive as next-day-mail at the Cleveland Clinic Foundation (CCF). Packages are delivered directly to the Central Biochemistry Lab.

9.3.5 Communication with Participating Clinical Centers Concerning Sample Receipt Problems, Protocol Changes, etc.

The Central Biochemistry Lab will communicate sample receipt problems, protocol changes, and other information to the participating clinical center personnel as needed.

9.4 Sample Handling at the Clinical Centers

9.4.1 Sample Requirements

Table 9.1 lists the total volume of serum and plasma (2 serum separator tubes and 2 plasma tubes) are needed to complete the various biochemical assays. In general, 20 to 30 ml of blood will be required. The table includes tubes and volumes for biochemistry assays done at the Central Biochemistry Laboratory. The volume indicated does not allow for rechecking any tests by the CBL.

The sample requirements for the optional testing to be performed by the local laboratories may vary among the clinical centers and should be determined for each site. Table 9.1 of the MOP may be copied and posted in your blood drawing area for easy reference. There are lines on it that can be filled in with the amounts required for local laboratory tests.

9.4.2 Labeling

All mailing tubes should be labeled with the participant's ID number, name code, date, and visit number. Urine aliquots must also have the total volume on the label.

Use waterproof pen to write on the label and cover the label with attached tape to ensure that the writing will not smear. Double check to be sure the numbers and letters are clear and legible.

To use the orange freezer safe labels, flip back the cellophane to expose the orange label. Be careful not to completely remove the cellophane. Print legibly the participant's ID number, name code, date, visit number, and 24 hour volume (green top tubes). Remove the backing from the orange label to expose the adhesive surface. Apply the right side of the label to the tube, wrap the label around the tube, and now remove the backing from the cellophane and wrap it tightly over the orange label. Be sure to label the tube with the orange freezer label before it is frozen.

IMPORTANT: DO NOT WRITE CLOSE TO THE RIGHT EDGE OF THE ORANGE LABEL. OTHERWISE, THE WRITTEN INFORMATION ON THE LABEL WILL BE OVERLAPPED WHEN THE LABEL IS APPLIED TO THE MAILING TUBE.

9.4.3 Instructions for Drawing Blood for Biochemistry Samples

The patient should be fasting at least 10 hours before annual visit blood draws. The patient should be instructed to avoid medications listed in Appendix 1 for at least 2 days preceding a blood sample. The subject should be seated during venipuncture. Blood should be drawn from an antecubital vein, or failing this, from some other convenient arm vein. Hot packs (hot towels wrapped in absorbent pads) may bring up veins when none are apparent. The best policy is to take time to choose a good site initially. A tourniquet (e.g., an 18 inch length of Davol #9794 one-inch diameter Penrose drain tubing) or blood pressure cuff should be released prior to withdrawal of the blood sample, and at no time should it be left

on for more than 3 minutes. Blood is drawn using the Vacutainer system following the instructions supplied with the system. A one-inch, 21 gauge needle is suggested. The needle should be placed in the vein. The required number of Vacutainer tubes should be filled as completely as possible. If, for some reason, a tube is not completely filled, an extra tube of blood should be drawn and combined specimens sent.

9.4.3.1 Processing Serum (Form 122) for Central Biochemistry Lab Analysis

1. Record identifying data on Form 122.
2. Allow the blood to clot at room temperature for at least 30 minutes.
3. Spin down all tubes in a bench top centrifuge.
4. Pour or pipet the serum into mailing tubes. **DO NOT COMPLETELY FILL** the tubes – leave an air space to allow for expansion during freezing. Refer to Table 9.1 for clarification of amount needed at each visit. Fill out the tube label and place on the mailing tubes.
5. Close lids tightly. Place tubes in freezer, -20°C or colder. **If tubes are shipped the same day as drawn at the clinical center, they do not have to be frozen. However, store in refrigerator until ready to package for same day shipment.**
6. Serum must be received at the CBL \leq 7 days from the draw date if the sample is not frozen. If the sample is frozen, the serum must be received at the CBL \leq 30 days from the draw date.

9.4.3.2 Frozen Plasma Sample (Form 127) that is Shipped on Dry Ice to the CBL

These instructions are for the collection and processing of a special-handling lavender tube drawn at C12, C24, C36, C48 and C60 using Form 127 (CBL Dry Ice Mailing Form).

At the C12 and subsequent annual visits, please follow the collection and processing instructions below:

1. The Frozen Plasma Sample is collected at C12, C24, C36, C48 and C60 (patient must be fasting visit at least 10 hours). If a patient reaches dialysis prior to their first dry ice shipment at C12, the special frozen plasma sample is the first blood drawn as soon as possible after dialysis is started. However, for those dialysis patients who had a frozen plasma collected prior to the start of dialysis, a frozen plasma sample is no longer collected post dialysis.
2. Special mailing Cryovial tubes that will be provided by the Central Biochemistry Laboratory (CBL) will be used for this collection.

3. These specimens will be kept frozen and shipped in batches to the CBL.
4. These specimens **MUST** be shipped SEPARATELY from the other CBL specimens using DRY ICE.
5. Lastly, this sample should **not** be collected during a home visit since timing is vital to the accuracy of the sample. Also, the time from collection to the time the sample is placed in the freezer should not be more than 1 hour.

Procedure for the Collection and Processing of the C12, C24, C36, C48 and C60 Frozen Plasma Sample (Form 127) that is Shipped on Dry Ice to the CBL:

1. Follow the Instructions for drawing Blood for Biochemistry samples in section 9.4.3 of the Manual of Operations for drawing the 10 mL lavender top tube.
2. Draw the lavender top tube at the same time as the other tubes for the C12 and annual visits as listed in Table 9.1 of the MOP.
3. Centrifuge the lavender top tube as quickly as possible in a bench top centrifuge.
4. Remove the lavender top tube from the centrifuge as soon as the centrifuge has stopped spinning. **Do not leave the tube sitting in the centrifuge.**
5. When the lavender top tube is taken out of the centrifuge, remove the plasma using a pipette, taking care not to disturb the red cells. (If the top of the red cell layer is disturbed, you must re-centrifuge the lavender top tube.)
6. Dispense the plasma in equal portions of a maximum of 1.0 mL of plasma into the four “Special Cryovial Mailing Tubes” that are supplied by the CBL.
7. Close (screw) the top tightly. Affix one of the special labels that are pre-labeled with the patient’s name code and identification number to each tube. Make sure to write in the visit number in the space provided on the label.
8. Place the four tubes in the freezer as soon as Step 7 is completed. **Do not leave these tubes sitting out at room temperature or in the refrigerator. The time from collection to the time the sample is placed in the freezer should not be more than 1 hour.**
9. Complete the CBL Dry Ice Mailing Form #127 and data enter the form only when the sample has been shipped to the CBL.

10. Batch and ship these special frozen plasma samples to the CBL according to the special dry ice shipping instructions.

Note: For home visits, you may collect a lavender tube and process in the normal manner per the MOP, section 9.4.3 and section 9.4.3.1, using Form 122. However, the special frozen and dry ice plasma sample (Form 127) will need to be collected at a time when the patient can come to the clinical center to have this sample drawn.

9.4.4 24-Hour Urine Collection

Participants will be given urine collection equipment and instructions for collection prior to each collection. Urine should not be collected during a short-term illness. **If aliquot is shipped the same day as received at the clinical center, it does not have to be frozen. However, store in refrigerator until ready to package for same day shipment.** The urine should be refrigerated after it has been mixed, measured and aliquoted and must arrive at the CBL ≤ 7 days from the draw date if the sample is not frozen. If the sample is frozen, the urine must be received at the CBL ≤ 30 days from the date the collection started.

From each collection, aliquots will be stored at the CBL.

The AASK Research Technician or Study Coordinator will complete the Urine Mailing Form #123. Participants will be queried about the completeness and accuracy of each urine collection. It is important to ascertain whether the urine collection is accurate and complete (i.e., if the participant remembers to discard the first urine sample and collect all of the urine for the next 24 hours). Otherwise, the urine should not be sent to the CBL and the participant should collect another 24-hour urine.

9.4.4.1 Instructing the patient on collecting their 24-hour urine

1. Review with the patient the 24-hour urine collection instructions in Appendix 1.
2. Make sure they clearly understand the following points:
 - a. The liquid in the jug is a preservative, and must always be present in the jug. The preservative must not be discarded or washed out of the jug.
 - b. The first urine sample is not saved, but the time of this first urination is the beginning time for the collection.
 - c. Every urine sample during the 24-hour time period must be saved.
 - d. The patient must try to urinate 24-hours from the time the collection was started. This urine must be saved. If they cannot urinate at this time, this time is still used as the ending time.
 - e. If possible, the jug should be kept in a refrigerator during the collection period. Extreme temperatures are to be avoided.
3. Discuss with the patient which day during the month the collection should be started, and when the urine should be brought to the clinic. The patient should

not be menstruating during the collection. If menses are irregular and occur at the time scheduled for collection, collection should be postponed until after the period is finished.

4. Discuss with the patient the importance of collecting all of their urine during the 24-hour time period. Let them know that it is not the quantity of urine that is important. What is important is that every drop of urine is saved. The test results will then accurately reflect what their kidneys are doing.
5. The patient should be instructed to avoid medications listed in Appendix 3 for at least 2 days preceding a 24-hour urine collection.

9.4.4.2 Acceptance of 24-Hour Urines

1. “The 24-hour Urine Checklist” (Appendix 2) should be completed by the technician when the urine is brought to the clinic. If this is not possible, one of the other members of the study team should take on this task.
2. If any “incorrect procedures” are checked off the list, the urine should not be sent to the CBL for analysis. It is better to have missing data than incorrect data in the database. The collection should be rescheduled as soon as possible.

The following criteria must be met:

- a. The urine jug should have contained the acid preservative. In rare instances, the preservative may be added when the urine is brought to the laboratory, provided that it is brought in on the day the collection is completed.
 - b. Starting and ending date and time must be confirmed. The urine collection time must be within 23.0 and 25.0 hours.
 - c. The patient should have emptied their bladder at the “start time” and discarded this sample.
 - d. Every urine sample during the 24-hour time period must have been saved.
 - e. The patient should have emptied their bladder at the “ending time” and saved this urine.
 - f. The patient should not have had a short-term illness during the collection.
 - g. The patient should not have been menstruating during the collection.
 - h. The patient should have drunk the usual amount of fluids and eaten the usual amount of food during the collection period.
 - i. The jug should not have been frozen or overheated. Refrigeration during the collection is recommended.
3. If the technician discovers any information that may indicate that the urine was improperly collected, they should write this information on the checklist. The completed checklist is filed in the patient’s file.

4. Any questions about 24-hour urine collections should be directed to the CBL for clarification.

9.4.5 Processing the 24-hour Urine Samples for Central Biochemistry Analysis

1. Tighten the urine container lid and mix the sample well (invert container thoroughly at least 5 times) to evenly distribute the acetic acid preservative and other components that may have settled upon standing. If two containers were used to collect urine, the urine in each container must be thoroughly mixed; then the two must be thoroughly mixed together before the aliquot is taken off. A large (2 gallon) container will be needed to mix larger volumes of urine.
2. Measure the total volume of urine including amount of acid, but read below any foam that may be present. Look at the cylinder at eye level to read the correct total volume. Record volume on the tube and record identifying data and urine volume on Form # 123. **DO NOT SUBTRACT THE AMOUNT OF THE ACID.**
3. Pour an aliquot of urine into a 30 ml urine mailing tube. If the technician is unsure about his or her ability to pour this without spilling, a pipette with a bulb can be used. **DO NOT COMPLETELY FILL TUBES** – leave air space to allow for expansion of specimen during freezing.
4. Close the lid tightly. Fill out the tube label and place on mailing tube. Place tube in freezer (-20°C or colder). **If aliquot is shipped the same day as received at the clinical center, it does not have to be frozen. However, store in refrigerator until ready to package for same day shipment.**
5. Fill out Form # 123 and mail with aliquots of urine.
6. Urine must be received at the CBL ≤ 7 days from the start of collection if the sample is not frozen. If the sample is frozen, the urine must be received at the CBL ≤ 30 days from the start of collection.
7. Store 25 ml aliquot locally. This may be discarded once sample has been analyzed by the Central Laboratory.

9.4.6. Acetic Acid Preparation for 24-Hour Urine Collection

A preservative must be added to all 24-hour urine jugs before collection. The preservative for the urines is 5% acetic acid, 250 ml in every 4 liter urine jug. If a 4 liter jug is not available, a 1 gallon jug may be used with 250 ml preservative. The use of smaller containers for the 24-hour collection is discouraged.

Use of prepared 5% acetic acid is recommended. However, one can make 5% acetic acid as follows:

1. Use a graduated cylinder of 250 ml or greater volume.
2. Put about 200 ml of distilled water into the cylinder. DO NOT USE TAP WATER.
3. Add 12.5 ml of reagent grade glacial acetic acid. USE CAUTION, THIS IS STRONG ACID. ALWAYS ADD ACID TO WATER.
4. Add water up to the 250 ml mark on the cylinder.
5. Mix well.
6. Transfer to a tightly sealed bottle or urine jug. This solution may be made up well in advance and stored in the urine jugs as long as they are kept tightly closed. In the patient education materials, there is an instruction form for collecting 24-hour urine. Use this to provide instructions to the patient (Appendix 1).

9.4.7 Clinical Center Local Laboratory Specimens

1. Record identifying data on Form 113.
2. Obtain blood samples according to the requirements of the local laboratory.

9.4.8 Sample Storage

All CBL specimens (serum, plasma and 24-hour urine aliquots) should be mailed at the same time. Samples must not be mailed on Friday or before Holidays, since there is no one available to receive and process the samples in the Cleveland Clinic Foundation mailroom on weekends or Holidays. All filled mailing tubes must be kept frozen (-20°C or colder freezer) until they are shipped with an ice pack in the styrofoam mailers. **If specimens are shipped the same day as received or drawn at the clinical center, they do not have to be frozen. However, store in refrigerator until ready to package for same day shipment.**

After the CBL specimens are analyzed, they will be aliquoted and frozen at -70°C at the CBL.

9.4.9 Sample Mailing Instructions

Make sure to send all CBL samples and accompanying forms to the CBL lab. Place all biochemistry samples in a zip lock bag. Place two paper towels in these bags to absorb any leakage that might occur. These bags should be flattened by hand to remove air, sealed, placed with an ice pack, and placed into the styrofoam mailing container. Study forms (Form 122 or Form 123) may be placed into the styrofoam box, in which case they should also be in individual Ziplock bags to protect them from sample leakage and/or condensation from the ice pack. A better approach is to include the paper work in the mailer by laying the forms (unfolded) on the top of the styrofoam box. No ziplock bag is needed in this case. The lid is put on, and the styrofoam box is slipped into the cardboard outer mailing box.

This box is sealed with packing tape. All CBL samples should be sent by a next day express service to the CBL address. Do not send samples so that they would arrive on a weekend, i.e., do not ship on a Friday.

9.4.10 Instructions for Shipping SDS on Dry Ice

It is currently required that all individuals handling/shipping specimens on dry ice be trained and certified to ship “Dangerous Goods.” Centers should contact their local institution regarding the availability of this training.

The procedure for packaging and shipping the special frozen specimens to the CBL is as follows:

1. Remove specimens from the freezer. The CBL recommends that no more than 20 tubes be shipped in one batch. **Do not let the samples thaw.**
2. Place specimens in a biohazard bag and seal.
3. Place the bag with paper towels in another biohazard bag and seal.
4. Fill the shipping container about half full of dry ice. **Reminder: dry ice is very cold and should be handled with insulated gloves.**
5. Place the double bag containing the specimens on the dry ice.
6. Fill the remaining space of the container with dry ice.
7. Close and seal the container. The container must have the following stickers on the box:
 - Diagnostic Specimen
UN3373, the diamond on the label must point down
8. Fill out the UN1845 “diamond” sticker with your name and address in the lower left part of the sticker under “Shipper’s Name and Address.” Fill out the “Consignee Name and Address” on the lower right of the sticker with:
 - The Cleveland Clinic
East 96th & Carnegie Avenue
Cleveland, OH 44195
9. On the upper right of the sticker, #3, write 1 for the number of packages and 2.0 kgs. for the weight of the dry ice.
10. Remove the backing from the diamond sticker and place on the side of the shipping container. The diamond sticker label and the UN3373 sticker must both be on the same side of the mailing box, making sure not to overlap the stickers.
11. Please use the pre-labeled Fed-Ex air bill. Section 6 of the air bill should have the box marked that says “Yes, Shipper’s Declaration Not Required.” Please also check the Dry Ice box and write in the number of boxes and the weight of the box (2.0 kgs).
12. Ship to the Central Biochemistry Laboratory.

Appendix 1

Patient Instructions for the 24-Hour Urine Collection

You will need:

A container for urine collection will be given to you in the Clinic. The liquid in the jug is a preservative and should not be discarded or washed out.

The day before you bring urine in:

1. Start your urine collection preferably in the morning. Void, do not save this sample but write the time and date on your jug.
2. Save every bit of urine all day and all night. Put it in the container.

The day you bring the urine in:

1. At the time noted the day before, void and save this urine. This completes your 24 - hour collection. Write the time and date of completion on your jug.

This finishes your 24-hour collection.

2. Bring container to: _____

Things you will need to know:

1. Keep the jug of urine in a refrigerator, if possible. Avoid exposure of the urine to extreme temperatures.
2. Drink only as much liquid as usual.
3. If you're going to have a bowel movement, first pass your urine and save it so none will be lost.
4. Close the container securely and carry upright so it will not spill. A shopping bag makes this easier.

**If you have any questions,
telephone:** _____

Appendix 2 24-Hour Urine Collection Checklist

Patient's Name _____

Date _____ Visit _____

When the patient returns a 24-hour urine, ask the patient the questions underlined below. The notes after each question indicate the correct procedures and should **not** be read to the patient. Check one box for each of question 1-9. The criteria for completing question 9 are found in the Manual of Operations.

Patient Followed:

Correct Procedures	Incorrect Procedures	
-------------------------------	---------------------------------	--

- | | | |
|-------|-------|--|
| _____ | _____ | 1. Did the jug contain any liquid (even a small amount) before you started collection? Note: The jug should have contained a small amount of liquid preservative. The patient should have kept the preservative in the jug. |
| _____ | _____ | 2. <u>At what date and time did you begin and end the collection?</u> Note: There should be no less than 23 hours and no more than 25 hours between the start and end of the collection. The dates and times stated should match those on the jug. |
| _____ | _____ | 3. <u>How did you start the collection?</u> Note: The patient should have emptied his/her bladder, discarded the urine, and marked the time and date on the jug. |
| _____ | _____ | 4. <u>How did you proceed with the collection?</u> Note: The patient should have saved urine in the jug <u>every time</u> he/she emptied his/her bladder and not spilled or splashed any urine out of the jug. |
| _____ | _____ | 5. <u>Were there any times when you did not save urine in the jug? If so, how many times?</u> Note: The patient should have saved every urine. |
| _____ | _____ | 6. <u>Was there anything unusual about the day of the collection?</u> The patient should have drank the usual amount of fluids, eaten the usual amount of food, not felt ill (including cold, flu, any illness or infection), and not have been menstruating. |
| _____ | _____ | 7. <u>How did you end the collection?</u> Note: The patient should have emptied his/her bladder, saved the urine in the jug, and marked the time and date on the jug. |
| _____ | _____ | 8. <u>Where did you store the jug after ending the collection?</u> Note: If possible, the jug should have been stored in the refrigerator. The jug should not have been frozen or overheated such as when stored in a car during the heat of summer or in below freezing temperatures. |
| | | 9. _____ Urine is acceptable _____ Urine is unacceptable |

COMMENTS

Appendix 3
List of Some Common Medications That You Cannot Take 2 Days Before
a 24-Hour Urine Collection Test or Serum Measurements

TRADE (Brand) NAME	GENERIC NAME
Pain Medications	
Anacin	aspirin(acetylsalicylic acid)
Arthropan	salicylate salts
Bufferin	aspirin
Clinoril	sulindac
Dolobid	diflunisal
Empirin	aspirin
Feldene	piroxicam
Indocin	indomethacin
Medipren	ibuprofen
Motrin.....	ibuprofen
Naprosyn.....	naproxen
Various manufacturers	oxyphenbutazone
Rufen	ibuprofen
Disalcid	salsalate
Zorprin	aspirin
Advil.....	ibuprofen
Anaprox	naproxen sodium
Ecotrin	aspirin
Excedrin	acetaminophen/aspirin
Nalfon.....	fenoprofen calcium
Meclomen	meclofenamate sodium
Nuprin	ibuprofen
Butazolidin.....	phenylbutazone
Ponstel.....	mefenamic acid
Soma Compound.....	carisoprodol/aspirin
Tolectin	tolmetin sodium
Voltaren.....	diclofenac sodium
Antibiotics	
Anspor.....	cephradine
Ceclor	cefaclor
Keflex.....	cefalexin
Velosef	cephradine
Duricef	cefadroxil
Ultracef.....	cefadroxil
Cefadyl.....	cephapirin

TRADE (Brand) NAME**GENERIC NAME**

Keflin	cephalothin
Ancef	cefazolin
Kefzol.....	cefazolin
Mandol	cefamandole
Mefoxin.....	cefoxitin
Zinacef	cefuroxime
Monocid	cefonicid
Precef	ceforanide
Cefotan.....	cefotetan
Claforan.....	cefotaxime
Cefizox.....	ceftizoxime
Cefobid.....	cefoperazone
Moxam	moxalactam
Rocephin	ceftriaxone
Fortaz	ceftazidime
Tazidime	ceftazidime
Tazicef.....	ceftazidime
Suprax	cefixime

Anti-Ulcer Agents

Alka-Seltzer	antacids/aspirin
Tagamet.....	cimetidine
Axid.....	nizatidine
Pepcid.....	famotidine
Zantac.....	ranitidine

Urinary Tract Anti-Infectives

Bactrim.....	trimethoprim/sulfamethoxazole
Septra	trimethoprim/sulfamethoxazole
Co-Trimoxazole.....	trimethoprim/sulfamethoxazole
Cotrim	trimethoprim/sulfamethoxazole
Trimplex	trimethoprim
Proloprim	trimethoprim

All nonsteroidal anti-inflammatory agents (including aspirin), cimetidine, ranitidine, trimethoprim/sulfamethoxazole, and trimethoprim must be withheld prior to a 24-hour urine collection or a blood test. This list only includes examples.

CHAPTER 10. CENTRAL BIOCHEMISTRY LABORATORY SAMPLE COLLECTION AND HANDLING

10.1 Calculation of Sodium, Potassium, and Protein Intake, Protein/Creatinine Ratio and Creatinine Clearance

Calculation of sodium, potassium, albumin, urea, protein intake, protein/creatinine ratio and creatinine clearance is based on the 24-hour urinary excretion of sodium, potassium, albumin, urea, protein and creatinine, respectively. The 24-hour urine collection Form #125 will report the 24-hour sodium, potassium, albumin, urea, protein and creatinine appearance in the urine.

The sodium excretion in the 24-hour urine collection will be reported as grams per 24 hours and as millimoles per 24 hours.

The potassium excretion in the 24-hour urine collection will be reported as grams per 24 hours and millimole per 24 hours.

The albumin excretion in the 24-hour urine collection will be reported as milligrams per 24 hours.

The protein excretion in the 24-hour urine collection will be reported as milligrams per 24 hours.

The creatinine excretion in the 24-hour urine collection will be reported as milligrams per 24 hours.

The 24-hour urine urea appearance will be reported on the 24-hour urine Report #193 as grams per 24 hours. The estimated protein intake can be calculated using this number in the following formula $([0.031] \times [\text{weight in kg}] + 24 \text{ hour urinary urea appearance}) \times 6.25$. Divide by the weight in kg = estimated protein intake.

The CBL will still do an estimated protein and creatinine clearance intake based on available data.

10.2 Sample Processing at the CBL

10.2.1 Sample Receipt and Log-In

CBL Technician Responsibility

- a. Record the receipt of the sample in the CBL sample log-in book.
- b. Check Forms 122 and 123 and all sample tubes closely for any errors, discrepancies or other problems. Record these in the Problem Log (Section 10.5).
- c. Notify the clinical centers by FAX, phone or electronic mail of any problems.
- d. All analyses should be completed within three business days following receipt of the samples.

- e. Any samples which are left over after analyses are completed will be aliquoted and stored frozen at -70°C . for future testing.

10.2.2 Sample Distribution by the CBL Technician

- a. Run QC appropriately or as procedure manual requires.
- b. Label tubes with ID name code, number, date of the sample, and visit.
- c. Put required amount of sample in each tube.
- d. Urine samples for urea nitrogen must be diluted 1:11 with Saline diluent.
- e. Hand carry the samples to the appropriate areas in the laboratory.
 - 1. Serum:
 - a. Hitachi Modular Analytics and Beckman CX3 Delta. CHEM PANEL, Cholesterol, HDL-cholesterol, and triglycerides
 - b. ToSoh Medics NexIA – Insulin
 - c. Dade Behring, BNII C-Reactive Protein
 - d. Abbott, IMX (2002-2003) – Homocysteine
Bayer, Centavr (July 8, 2004 – present) - Homocysteine
 - 2. 24-hour Urine Aliquot:
 - a. Beckman CX3 Delta - Creatinine, Potassium, Sodium-5 mL urine Aliquot; and Urea Nitrogen (dilution).
 - b. Manual section - Protein (TCA-Ponceau S method).
 - c. Dade Behring, BNII- albumin
 - 3. Plasma:
 - a. Inflammatory Markers – To be Determined. Specimen will be split to 1.0 mL aliquots, labeled and frozen at -70°C .
 - 4. Fingernails:
 - a. Specimens will be frozen at -70°C .

10.2.3 Analytical Methods of the Central Biochemistry Laboratory

- a. Serum
 - 1. Chem Panel and lipid profile: Roche Modullar and CX3 Delta: See Modular Operations Manual and CX3 Delta Operations Manual. Note: creatinine measured by rate-Jaffe' methodology.
 - 2. Total Cholesterol and Triglycerides: Hitachi Modular Bichromatic Analyzer using Roche Enzymatic Assay systems. See Naito, H.K. and David, J.A. Lipid Research Methodology 1-76(1984), Alan R. Liss, Inc., New York.
LDL-cholesterol: The following calculation is used for LDL. $\text{LDL} = \text{cholesterol} - [(\text{Triglyceride divided by } 5) + \text{HDL}]$.
 - 3. Insulin: Enzyme ImmunoAssay (EIA).
 - 4. HSCRIP: immunonephelometry

5. Homocysteine: Fluorescence Polarization Immunoassay (FPIA) (2002-2003)
Homocysteine: Chemiluminescence Immunoassay (July 8, 2004-present)
- b. Urine
1. Protein: TCA-Ponceau S. See Pesce, MA and Strande, CS, Clinical Chemistry, 1973; 19-1265.
 2. Sodium, Potassium, Creatinine, and Urea: Beckman CX3 Delta methods. See Beckman CX3 Delta Operations Manual. Note: creatinine measured with rate-Jaffe' methodology.
 3. Albumin: Dade Behring – BNII, nephelometer
- c. Result Report
1. The technician who runs the Hitachi analyzer will return the samples along with the results to the CBL technician.
 2. The CBL technician runs the urine protein assay and the Beckman analyzer.
 3. Record the QC and precision results in the core lab QC book.
 - a. Review QC results.
 - b. If out of range, write up discrepancy report and take corrective action, in accordance with CCF QC guidelines.
 4. Calculate proteins to mg/dl.
 5. Write up Forms 124 and 125 for each patient, as needed.
 6. All calculations and data records are visually rechecked for transcription errors.
 7. Forms 124 and 125 are transmitted electronically to the DCC and Reports 192 and 193 to the clinical center. Record the data sent to the DCC in the log-in book.
 8. Keep the original result print out.

10.3 Internal Quality Control Protocol for the CBL

Currently, about 15% of the patient sample load constitute QC samples. Usually there are two to three known concentrations from several vendors, depending on the biochemical constituent being measured.

10.4 QC Action Guidelines

10.4.1 Daily Quality Control Action Procedures

1. Two Controls
If two controls are used and if one control result is within the 2 S.D. limits and one control is between 2-3 S.D. limits, the run is acceptable. Results can be reported.

2. Two Controls

If two controls are used and if one control result is within the S.D. limits but one control is outside the 3 S.D. limits, OR if both results fall outside the 2 S.D. limits, the run is unacceptable.

- a. Do NOT report results from the run.
- b. Take corrective action that may include but is not limited to the following:
 - 1) Re-running control(s); the results are within expected limits.
 - 2) Re-running patient samples from an acceptable run; the results are within expected proficiency limits.
 - 3) Re-running selected patient samples from the unacceptable run on an alternate instrument; the results are within expected proficiency limits.
 - 4) Re-running control(s) and selected patient samples from the unacceptable instrument in which the control results are within the expected limits.
 - 5) Re-running the entire unacceptable run on the same or an alternate instrument in which the control results are within the expected limits.

NOTE: Re-running of control(s) can include

- 1) The same control(s)
 - 2) Freshly reconstituted control(s)
 - 3) Control(s) from another section/area
 - 4) Repeating the pre-step procedure with control(s)
- c. Notify the supervisor/staff if the problem cannot be resolved.
 - d. Do not release patient results until the problem has been corrected and QC is acceptable for the run or an alternative procedure is employed. Verify and record ALL corrective action (examples of corrective action documentation are listed at the end of the Daily Quality Control Action Procedure).

3. More than Two Controls

If more than two controls are used and if two (2) or more of the control values fall outside the 2 S.D. range or one (1) or more fall outside the 3 S.D. range, the run is unacceptable.

- a. Do NOT report results from the run.
- b. Take appropriate corrective actions as described in Section 2b.
- c. Notify the supervisor/staff if the problem cannot be resolved.
- d. Do not release patient results until the problem has been corrected or an alternative procedure employed. Verify and record ALL corrective action (examples of corrective action documentation are listed at the end of the Daily Quality Control Action Procedure).

4. One Control

The use of one level of control run once is acceptable for only electrophoresis. If the control result is outside the 3 S.D. limit, the method QC is unacceptable.

- a. Do NOT validate the run. Discontinue running patient specimens until the method demonstrates acceptable QC.
- b. Take appropriate corrective actions as described above in section 2b.
- c. Notify the supervisor/staff if the problem cannot be resolved.

- d. Do not release patient results until the problem has been corrected or an alternative procedure employed. Verify and record ALL corrective action (examples of corrective action documentation are listed at the end of the Daily Control Procedure).

Examples of Acceptable Documentation (lettered for coding purposes):

- a. Run unacceptable
- b. Run repeated
- c. Rechecked control(s)
- d. No patients reported
- e. Repeated patients on alternate instrument
- f. Performed patient rechecks on same/alternate instrument

10.4.2 Shifts and Trends

If QC results indicate a shift and/or trend:

1. Take action that includes but is not limited to the following:
 - a. Investigate method and/or control performance
 - b. Recalibrate
 - c. Perform calibration verification
 - d. Check reagent integrity
 - e. Process proficiency specimens
 - f. Evaluate alternate control material
 - g. Verify control limits
 - h. Evaluate instrument performance
 - i. Contact manufacturer
 - j. Evaluate inter-method performance
2. If investigation indicates potential incorrect patient results, do not release patient results until the problem has been corrected or an alternative procedure employed.
3. Document all summary and detail of correction action on the QC log sheet. Retain all supporting documentation.

10.5 AASK CBL Problem Record

Date	Date Msg Sent	Center	Problem	Response	Tech

10.6 Reference Ranges For The Central Biochemistry Laboratory

<u>Serum</u>	<u>Sex</u>	<u>Range</u>	<u>Units</u>
Insulin		1.0-24.0	uU/mL
C-Reactive Protein		0-.3	mg/dL
Homocysteine	M	7.4-15.7	umol/L
Homocysteine	F	3.9-14.8	umol/L
T. Protein		6.0-8.4	g/dL
Albumin		3.5-5.0	g/dL
Magnesium		1.6-2.4	mg/dL
Phosphorus	(Adult)	2.5-4.5	mg/dL
Calcium		8.5-10.5	mg/dL
Creatinine		0.7-1.4	mg/dL
Glucose		65-110	mg/dL
Urea Nitrogen	M	10-25	mg/dL
Urea Nitrogen	F	8-25	mg/dL
Uric Acid	F	2.0-7.0	mg/dL
Uric Acid	M	3.0-8.0	mg/dL
T. Bilirubin		0.0-1.5	mg/dL
AST		7-40	U/L
LDH		100-220	U/L
Alk. Phos.	(Adult)	20-120	U/L
GGT	M	0-50	U/L
GGT	F	0-35	U/L
Sodium		135-145	mmol/L
Potassium		3.5-5.0	mmol/L
Chloride		98-108	mmol/L
Carbon Dioxide		24-32	mmol/L

<u>24-Hour Urine</u>		<u>Range</u>	<u>Units</u>
Creatinine	M	1000-2000	mg/24 hrs
Creatinine	F	800-1800	mg/24 hrs
Urea Nitrogen		12-20	g/24 hrs
Protein		<150	mg/24 hrs
Sodium		0.9-5.1	gm/24 hrs
		40-220	mmol/24 hrs
Potassium		1.2-3.9	gm/24 hrs
		30-99	mmol/24 hrs
Albumin		<30	mg/24 hrs

	<u>Lipid Reference Ranges</u>		<u>Risk Classification</u>		
	Age	Sex	Desirable	Borderline High	High
Total Cholesterol	<20	M,F	75-169	170-199	≥200
	≥20	M,F	100-199	200-239	≥240
LDL-Cholesterol	<20	M,F	50-99	100-129	≥130
	>20	M,F	60-129	130-159	≥160
HDL-Cholesterol	All	M	>45	36-45	≤35
	All	F	>55	36-55	≤35
Triglycerides	<15	M,F	25-120	121-299	≥300
	≥15	M,F	30-149	201-499	≥500

CHAPTER 11. ECHO STUDY MANUAL OF OPERATIONS FOR FIELD AND CORE LABS

11.1 Introduction to the AASK Cohort Study

Welcome to the echocardiography substudy of the African American Study of Kidney Disease and Hypertension (AASK) Cohort. The AASK study is greatly indebted to the investigators of the Cardiovascular Health Study (CHS), who generously shared the Manual of Operations from the CHS study. Much of the text and philosophy is directly taken from the CHS Manual of Operations. We thank the LIFE study for graciously sharing several figures (see appendix).

The AASK Cohort Study is a prospective, observational study that is an extension of the AASK randomized clinical trial that was conducted from 1994 to 2001 in African Americans with hypertension and mild to moderate renal dysfunction. The AASK trial tested the effects of 3 different medications used as first line anti-hypertensive therapy (ramipril, metoprolol and amlodipine) and 2 levels of blood pressure control (usual control and more aggressive control) on progression of renal disease. In brief, the study found that usual blood pressure control was as effective as aggressive control in preventing progression of renal disease, and that as first line therapy, the converting enzyme inhibitor ramipril was superior to the other agents for preventing progression of renal disease.

Of the 1,094 randomized participants in AASK, we anticipate that 650-750 individuals who have not reached end-stage renal disease (ESRD) will enroll. In addition, those individuals who reached ESRD during the AASK trial will be invited to attend one visit for collection of DNA. Twice each year, approximately every 6 months, exposures will be collected. Exposures will include environmental, genetic, physiologic, and socio-economic factors. The primary renal outcome will be a clinical outcome defined by doubling of serum creatinine, ESRD or death. Appropriate anti-hypertensive treatment (medications and target BP level as determined in the AASK trial) will be provided to all participants who do not have ESRD. In this fashion, the cohort will directly control two of the major 'known' determinants of kidney disease progression (treatment of hypertension and use of reno-protective, anti-hypertensive medication) and will therefore address research hypotheses in the setting of recommended anti-hypertensive care. We anticipate a minimum of 4 contacts and maximum of 6 contacts per year for BP control. The minimum duration of follow-up in the Cohort Study will be 5 years (total of 10-12 years, including the period of the AASK trial).

The primary objective of the AASK Cohort Study is to determine prospectively the long-term course of kidney function and risk factors for kidney disease progression in African-Americans with hypertension-related kidney disease that receive recommended anti-hypertensive therapy. A secondary objective is to determine the occurrence of cardiovascular disease and assess its risk factors in the setting of hypertension-related kidney disease. The majority of the causes of death in patients with renal disease are due to cardiovascular events. Hence, determining the factors that predict these events is especially important.

11.2 Left Ventricular Hypertrophy as a Risk Factor for Cardiovascular Disease

Progressive renal dysfunction is associated with the occurrence of traditional and non-established risk factors for CVD. The contribution of hypertension to atherosclerosis and to left ventricular hypertrophy (LVH) is well known. LVH is the most common cardiac structural change seen in ESRD and its prevalence increases as renal function deteriorates. LVH is well known to be an independent risk for sudden cardiac death. The anemia that develops with progressive renal deterioration may also contribute to LVH and increased LVMI compromising coronary vasodilator reserve and together with a mismatch of cardiomyocyte mass and capillaries contributes to a tendency to myocardial ischemia^{1 2}.

Considered as a discrete, categorical variable, LVH significantly increases the risk of coronary artery disease, congestive heart failure (CHF), cerebrovascular accidents, ventricular arrhythmia, and sudden death in the general population.³⁻⁵ LVH increases the relative risk of mortality by twofold in subjects with coronary artery disease and by fourfold in those with normal epicardial coronary arteries.^{6,7} In addition, when LV mass is considered as a continuous variable, a direct and progressive relationship exists between cardiovascular risk and the absolute amount of LV mass. During 4 years of follow-up in the Framingham Heart Study, each 50 g/m increase in LV mass was associated with a 1.49 increase in relative risk of cardiovascular disease for men and 1.57 for women. The effect on cardiovascular mortality was even more striking, with a 1.73 relative risk for each 50 g/m for men and 2.12 for women.⁴ There is also increasing evidence that regression of LV mass reduces the incidence of cardiovascular events.⁸

The relationship between LV mass and cardiovascular outcome is not known in a population of African Americans with hypertension and mild to moderate renal disease. Furthermore, the predictive value of LV mass in such a population that is treated, as these patients will be, with angiotensin converting enzyme inhibitor as the basis of therapy, is not known. Therefore, the purpose of measuring LV mass in this study is:

- To determine if LVH at baseline predicts the occurrence of subsequent outcomes (CVD events and progression of renal disease)
- To determine if change in LV mass predicts the occurrence of subsequent outcomes (CVD events and progression of renal disease).⁸
- To determine factors which predict the progression of LV mass and the occurrence of LVH. Putative exposures include non-dipping status and nocturnal BP.

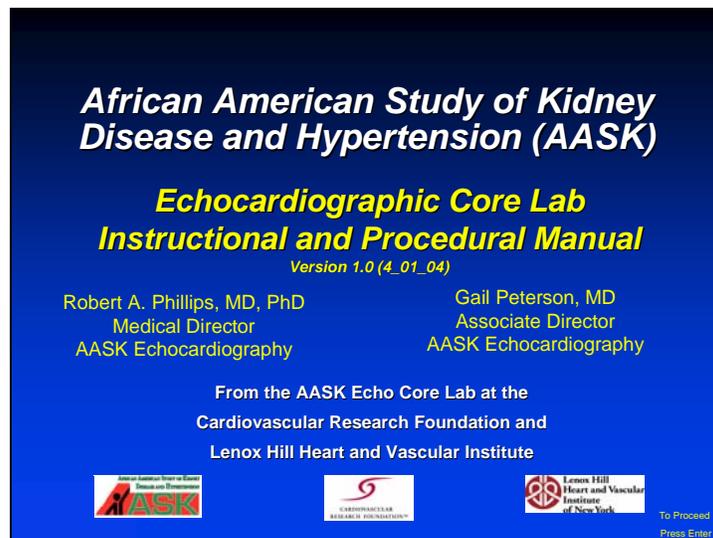
There is also evidence from previous studies that simply acquired measures of vascular and left ventricular compliance, as well as measures of global LV function are predictive of future cardiovascular events.^{9 10;11} The degree to which these measures may also identify a group at risk in the AASK Study will also be of great interest.

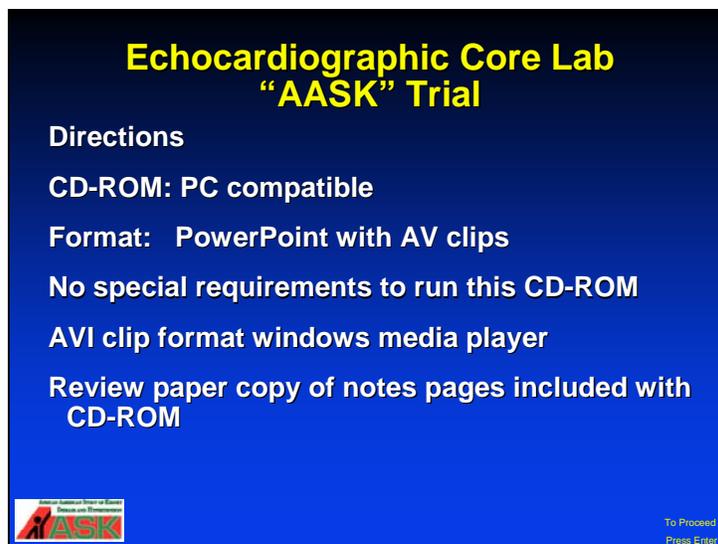
11.3 The Primary Objectives of Echocardiography in the AASK Cohort Limited Echo Study

The primary objectives of echocardiography in the AASK Cohort Limited Echo Study are to determine whether one or more of a limited number of echocardiographic or Doppler parameters of cardiac structure and function are useful in predicting cardiovascular events or progression of renal disease mortality or extent of disability in subjects who, during a five year follow-up, develop cardiac events (myocardial infarction, congestive heart failure, etc.) or cerebrovascular accidents.

Importantly, we will determine the importance of change in LV mass and LV function over a five-year interval as a predictor of new clinical events, i.e., stroke, heart attack and death. Cardiac structural parameters to be evaluated include left ventricular wall thickness and mass and left ventricular dimensions, while cardiac functional parameters include left ventricular percent fractional shortening, midwall fractional shortening, left ventricular wall stress and Doppler stroke volume, large vessel compliance (stroke volume/pulse pressure) and left ventricular filling parameters.

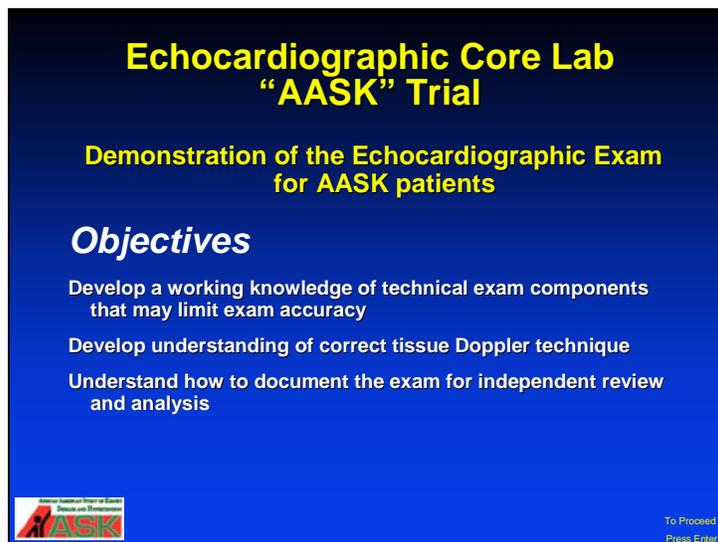
11.4 Echocardiographic Core Lab Instructional and Procedural Manual





A CD-ROM of these slides has been sent to the sonographers at each site, and includes moving images of example echocardiograms. This instructional CD-ROM is PC-compatible. Double click the power point presentation on the CD-ROM to open it. To view the program appropriately, click "slide show" (under "View", in the upper left screen). Once in the slide show, press enter to advance to the next slide. To run video clips you will need the upgraded version of windows media player. This is a free download if you presently use windows media player. If the slides with AVI clips show an image then go blank you do not have the required program to open the file and will need to download the program from the website. Go to website: <http://windowsmedia.com/9series/Download/download.asp>. Please call the Echo Core Lab if you need assistance viewing the instructional CD-ROM.

This section includes the slide set the sonographers received. As you proceed through the slide show, review the corresponding note pages (included in your packet) for additional explanations on many of the slides.



Echocardiographic Core Lab “AASK” Trial

Exam Goals and Trial Endpoints

- Determination of LV mass
- Evaluation of LV systolic and diastolic function and LV filling parameters
- Calculation of LV wall stress and large vessel compliance (stroke volume:pulse pressure ratio)



To Proceed
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Echocardiographic Core Lab “AASK” Trial

Echocardiographic Parameters Assessed

- 2-D acquisition and M-mode measurement of LA and Ao
- 2-D measurement of aortic annulus (for stroke volume calculation)
- 2-D directed M-mode measurement of LV mass and ejection fraction
- 2-D measurement of LV mass via area-length method (using PSAX and apical 4-chamber views)
- LV inflow (E and A waves) to assess LV diastolic filling
- Tissue Doppler of lateral annulus to assess diastolic function
- Flow velocity integral of LVOT (for stroke volume calculation)
- Heart rate (to determine cardiac output)
- Simultaneous measurement of blood pressure to allow calculation of wall stress and stroke volume/pulse pressure ratio



To Proceed
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2-D and M-mode Image Acquisition General Principles

- Record the echocardiogram with patients in the partial left decubitus position
- Clear ECG visible at bottom of screen
- Shallowest depth possible should be utilized
- Minimum 10 beats of each moving image and 5 seconds of each still frame recorded
- M-mode images performed initially with simultaneous 2-D update image, followed by full screen image, followed by at least 2 different freeze frame images



To Proceed
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1. Patients will be positioned in the left lateral recumbent position to optimize imaging of the LV and to help standardize the method for obtaining these images.
2. A clear ECG signal should be visible at the bottom of the screen.
3. The left ventricle should be imaged in the most magnified presentation (i.e. at the shallowest display depth that results in good endocardial definition). At deeper depths, the imaging information is represented by fewer pixels, and frame rates may be slower, both of which result in lower image resolution.
4. A minimum of 10 beats should be recorded of each image; a minimum of 5 seconds of each still frame should be recorded.
5. M-mode images will be performed initially in a format with simultaneous 2-dimensional update image. Then a full-screen image should be obtained of the M-mode (50 mm/sec sweep speed) during quiet respiration. Then two 5-second freeze-frame recordings of the full-screen M-mode will be produced at gently held-expiration with care taken to avoid a Valsalva maneuver or forcible exhalation.

2-D and M-mode Image Acquisition

General Principles

Appropriate Gain Settings

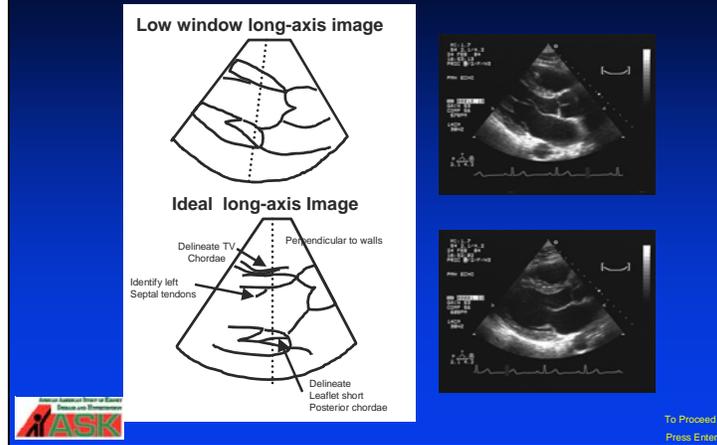
It has been noted that optimal definition of endocardial and epicardial interfaces for making measurements at the Echo Core Lab require using higher gain than is generally optimal for displaying these interfaces on the video monitor during performance of the study at the Field Center. The necessity for using higher gain to record images of the LV will be emphasized at frequent intervals to the Field Center technologists so that optimal recordings for interpretation at the Echocardiography Core Lab are obtained.



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The Echocardiography Core Lab will be making measurements from stop-frames recorded on videotape and/or on optical disk. It has been noted that optimal definition of endocardial and epicardial interfaces for making measurements at the Echo Core Lab require using higher gain than is generally optimal for displaying these interfaces on the video monitor during performance of the study at the Field Center. The necessity for using higher gain to record images of the LV will be emphasized at frequent intervals to the Field Center technologists so that optimal recordings for interpretation at the Echocardiography Core Lab are obtained.

2-Dimensional Imaging

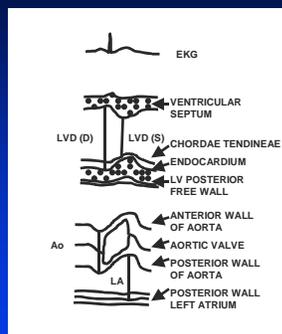


This shows an example of a low window parasternal long-axis, with the LV walls not perpendicular to the scan lines. If this image occurs, try to move 1 interspace higher and remember to maximize the LV size by panning medially and laterally, and clarify LV interfaces, to obtain a more ideal long-axis image. The selection of transducer frequency and focal length can influence endocardial definition. As a general rule, imaging should be performed with the highest frequency transducer that provides adequate penetration of the chest for good structural (especially endocardial) definition. In an individual with large amount of soft tissue or air between the transducer and heart, the lowest transducer frequency (2.5 MHz) will probably be necessary.

M-mode Imaging

ASE Standards

- Use thinnest continuous echo lines to denote the desired interface
- Measure dimensions and wall thickness from leading edge of the anterior echo line to leading edge of the posterior echo line
- Make diastolic measurements at the onset of the QRS complex
- Measure LV cavity and wall thickness at the level of the chordae tendinae below the MV.

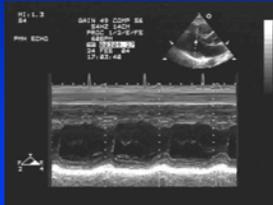


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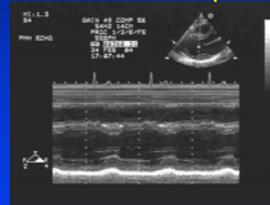
M-mode Imaging

- The LV should be as perpendicular as possible to the transducer
- It is very important to record identifiable and continuous echo lines for each of the relevant structures (e.g. recording an identifiable endocardial and epicardial line for the posterior wall of the LV)

Incorrect: off axis



Correct line up



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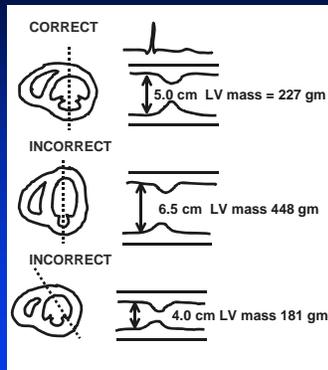
To measure the LV minor axis dimensions and parietal thickness accurately with M-mode technique it is necessary to orient the echocardiographic beam from the parasternal window to pass perpendicularly through the interventricular septum and posterolateral LV wall at the level of the junction of the papillary muscle tips and mitral chordae. This should be performed under two-dimensional guidance.

For accurate and reproducible measurement of these structures, dominant lines representing the necessary interfaces (the right and left sides of the septum and the endocardial and epicardial surfaces of the posterior LV wall) should exhibit continuous motion in the correct pattern from the structure for at least 0.10 sec, and should ideally do so throughout the entire cardiac cycle.

M-mode tracing of the left ventricle will be recorded at a speed of 50 mm/sec simultaneously with lead II of ECG in end expiration phase. The technologist should virtually count out the 10 beats during recording. A stable hand is important during this recording.

M-mode Imaging

- Improperly alignment results in large error variation (e.g. LV mass as shown adjacent)
- Avoid by
 - Keeping echo sector perpendicular to long-axis of LV
 - Place M-mode cursor through center of LV
 - May need to go up one interspace



To Proceed
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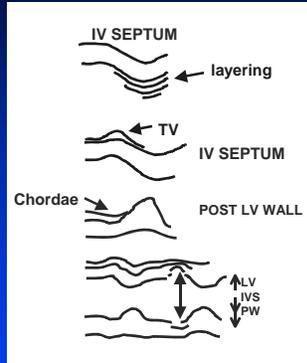
It is easy to improperly align the echo sector relative to anatomic axes, or improperly place the M-mode cursor during 2-D targeted recording of the LV. Such errors of acquisition technique can result in large error and variation in the measurement of LV mass. As shown in the figure, a “true” LV mass calculation of 227 gm may vary between 181 gm and 448 gm based on improper cursor or sector placement respectively. Inaccurate LV mass measurements may also result from a “low” window” If this shape LV occurs, try to move 1 interspace higher.

To avoid these errors, accurate echo technique aimed at proper direction of the transducer particularly in the parasternal short axis view is of paramount importance. In particular

1. The echo sector must be perpendicular to the long axis of the LV and
2. The m-mode cursor must pass through the center of the LV
3. Additionally, optimal definition of septal and posterior wall interfaces is desirable but usually less problematic than “angulation” errors.

M-mode Imaging Common Errors

- Low-window M-mode: LV septal echos "layer" in systole as upper ventricular septum is drawn into the oblique beam
- Including TV chordae with ventricular septum: right septal echos separate in late diastole (remember, solid muscle can't get thicker as it relaxes)
- Including MV chordae in posterior wall measurements (results in posterior wall appearing to thicken at end-diastole)
- If LV imaged medially or laterally to central plane, small thick-walled LV occasionally becomes larger, with thinner walls at end-diastole



To Proceed
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Several other types of errors can occur when imaging/measuring the LV. These include

1. Low-window M-mode manifested as layering of the septum in systole (figure above)
2. Including the tricuspid chordae in the measurement of the right septum (figure above). This is manifested as separation of the right septal echoes in late diastole, making the septum appear to thicken at end diastole. Since solid muscle does not get thicker as it relaxes (at end-systole), when it does thicken at end diastole it means that the LV septal imaging is including the tricuspid chordae.
3. Including mitral chordae in the posterior wall measurements. This is manifested as the posterior wall appearing to thicken at end-diastole.
4. Difficulty in defining the border between the posterior wall and pericardium
5. When the LV is imaged medially or laterally to its center plane – wall drop out occurs at end-systole, manifested as thinner walls at end-diastole.

Pulsed Doppler Flow Recording General Principals

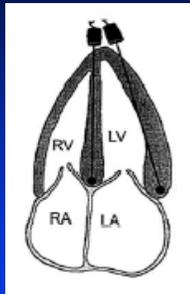
- Record beats demonstrating highest peak velocity and narrowest spectral dispersion of the velocity spectrum
- Pulsed Doppler measurements will not be performed from beats demonstrating maximum dispersion greater than 30% of the peak velocity.
- Record 10 beats with 2-D update image on screen along with Doppler recording, at 100mm/sec sweep speed
- Next record 10 beats full screen image
- Then record two 5-second freeze-frame images in gently held expiration



To Proceed
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Doppler images will be performed initially in a format with simultaneous 2-dimensional update image. Then a full-screen image should be obtained of the Doppler (100 mm/sec sweep speed). Then two 5-second freeze-frame recordings of the full-screen Doppler will be produced at gently held-expiration with care taken to avoid a Valsalva maneuver or forcible exhalation.

Tissue Doppler Imaging Background



- Measures high intensity low velocity echos of myocardium
- Sample volume 2-5 mm
- Sweep speed 50–100 mm/s
- Filters and baseline adjusted to low velocity range (-20 to 20 cm/sec) with minimal gain settings



To Proceed
Press Enter

While conventional Doppler focuses on low intensity and high velocity echos of blood flow, Pulsed wave Tissue Doppler Imaging (TDI) measures the high intensity low velocity echos of the myocardium. This figure shows placement of the pulsed Doppler sample volume at the lateral part of the mitral annulus for recording of velocities within the myocardial tissue in the apical four-chamber view.

Tissue Doppler Imaging TDI Pattern

- S_m systolic ejection phase
- E_m myocardial distension early diastole, surrogate of myocardial relaxation rate
- A_m passive myocardial distension by atrial contraction (retraction of the annular ring or due to ensuing late ventricular filling)

To Proceed
Press Enter

There are three distinct patterns of myocardial TDI obtained by proper imaging: forward systolic wave (S_m), early diastolic myocardial velocity (E_m) and an atrial contraction signal (A_m). These Doppler signals provide information on diastolic as well as systolic patterns, which are less influenced by various loading conditions on the heart than more traditional Doppler measurements.

Tissue Doppler Imaging Common Presets

	SONOS 5500	ATL	Acuson Sequoia
Power	0 Db	0 Db	0 Db
Gain	50-60%	50-60%	-6Db
Filter	50 Hz	low	2
Scale	± 25 cm/s	± 20 cm/s	± 20 cm/s
Gate length	0.56	0.4	0.25 cm
Compress	6		
Reject	8		
Edge			0
Sweep speed	50-100mm/s	medium	50-100mm/s
Dynamic Range			30 Db

To Proceed
Press Enter

Use predetermined settings for TDI (“TDI mode”) if available. This slide shows presets for some of the more common systems on the market, for reference. If predetermined settings are not available, decrease the PW Doppler gain (-15 to 20 decibels, Db) and use velocities filters to obtain low-frequency signals (myocardial tissue velocities are usually within 5-20 cm/sec range) and “filter-out” unwanted signal of blood velocities (range 70-120 cm/sec). Center that baseline so that full systolic diastolic signals are displayed. Harmonics mode should be used for imaging.

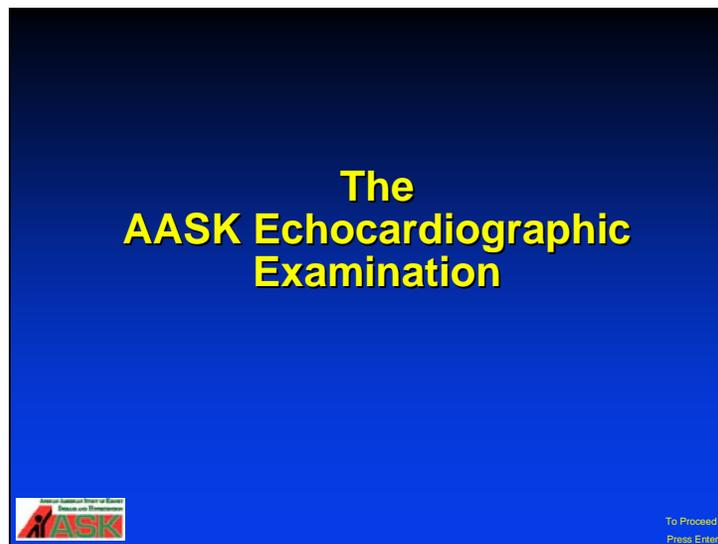
Tissue Doppler Imaging
Average lateral TDI velocities (cm/s)

<u>< 40 yrs</u>	
Em	17.3 ± 3
Am	8.7 ± 1.9
Em/Am	2.1 ± 0.6
<u>40-60 yrs</u>	
Em	16 ± 3.1
Am	10 ± 2.7
Em/Am	1.7 ± 0.6
<u>>60 yrs</u>	
Em	12.6 ± 3
Am	13 ± 3.4
Em/Am	0.95 ± 0.5



To Proceed
Press Enter

This slide shows average TDI velocities from the lateral mitral valve annulus, based on age, for reference. In young individuals the contribution of active myocardial relaxation to ventricular filling is dominant over atrial contribution. Therefore, Em is much higher than Am and Em/Am is > 1. With the normal process of aging, peak Em decreases and peak Am slightly increases. Em/Am transition to a ratio of < 1 occurs in patients over 60 years in the lateral wall.



AASK Echocardiographic Protocol

- The following information should be entered via the keyboard, displayed on the screen, and recorded on the videotape/optical disk:
 - Patient's AASK name
 - Patient's AASK identification number
 - Date of the study
 - Technologist code
 - AASK center number
- Attach the ECG electrodes
- Position the patient



To Proceed
Press Enter

AASK Echocardiographic Exam

- The echocardiography technologist should briefly describe the examination to the patient while the patient is being positioned on the table:
 - Ultrasound uses sound waves to take pictures of the heart and record flow through the heart and attached blood vessels
 - Test takes approximately 20 minutes, and should be painless except for mild pressure from the transducer
 - The patient may be asked to assume slightly different positions and breathing patterns during the test
 - Ultrasound gel used for recording the images may be cold. The ECG patches may cause some minor discomfort when they are removed.



To Proceed
Press Enter

AASK Echocardiographic Exam

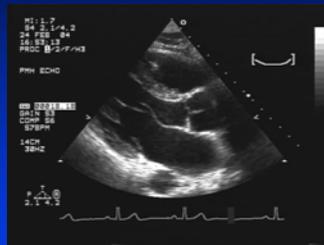
- The following images are examples of the minimum requirements by the Echocardiographic Core Lab for analysis of the echocardiograms. Remember to include additional information as necessary to document status of the intervention.
- A repeat exam may be required if the study does not meet these requirements. If you have questions at time of exam then we will have questions upon review



To Proceed
Press Enter

AASK Echocardiographic Exam *Aortic Annulus and Left Atrium*

- Place the transducer in 4th intercostal space, focusing on the aorta and LA
- Record 10 beats during quiet respiration

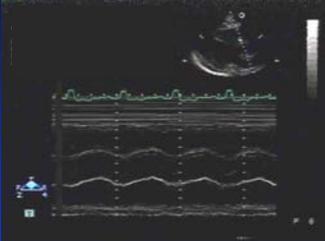


To Proceed
Press Enter

Place the transducer in the 4th intercostal space to obtain a parasternal long axis view. Two dimensional echocardiographic images should be performed at the level of the aorta and LA, with 10 beats recorded during quiet respiration.

AASK Echocardiographic Exam *M-mode aorta and LA*

- Place M-mode cursor through aorta and maximum dimension of LA. Display 2-D update image on screen along with M-mode image
- Record 10 beats moving image
- Record two 5-second freeze-frame images (shown)



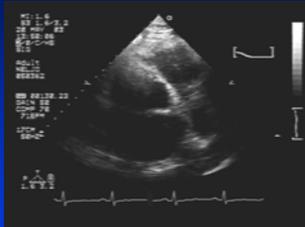
To Proceed
Press Enter

Next, the M-mode cursor should be positioned perpendicular through the aorta and the maximum dimension of the LA. The technologist should display the two-dimensional update image on the screen with the M-mode image of the aorta and LA.

Record 10 beats during quiet respiration. Next record 2 five-second freeze-frame images.

AASK Echocardiographic Exam *PSAX of aortic valve and LA*

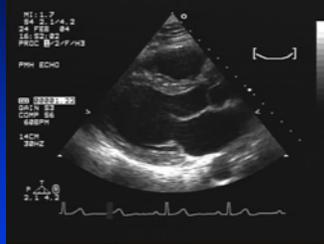
- Rotate transducer to obtain parasternal short axis image at the level of the aortic valve and left atrium.
- Record for 10 beats during quiet respiration.



To Proceed
Press Enter

AASK Echocardiographic Exam Parasternal Long Axis

- Transducer in 4th (and if needed 3rd) intercostal space
- Scan lines should be perpendicular to LV walls
- Adjust transducer to image the maximum vertical aspect of the LV
- Record 10 beats of a 2-D image



To Proceed
Press Enter

Rotate back to a parasternal long-axis view. Keep the transducer in the 4th (or if necessary the third) intercostal space and angle it to obtain good visualization of the interventricular septum and LV posterior wall in 2-D long-axis parasternal view (on short axis parasternal view at level of the chordae tendinae)

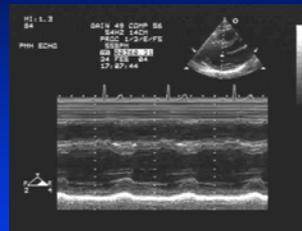
In an ideal long axis image the scan lines are perpendicular to the LV walls, the TV chordae and the MV leaflet short posterior chordae are delineated, the LV septal tendons are identified and the QRS on the ECG tracing is clearly evident.

In general, when imaging the heart in the PLAX view, one should attempt to adjust the transducer position such that the aorta is not angulated at its junction with the LV. Then, the transducer position should be adjusted to record the maximum vertical aspect of the LV.

Record 10 beats of a 2-D image from the parasternal view.

AASK Echocardiographic Exam PLAX M-Mode

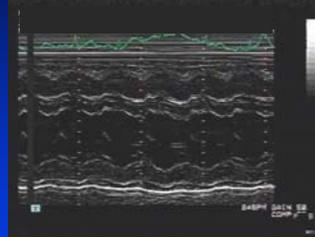
- Position M-mode cursor perpendicularly through LV cavity just below tips of mitral leaflets
- Display 2-D update image on screen with M-mode recording, at 50mm/s
- Record 10 beats during quiet respiration



To Proceed
Press Enter

AASK Echocardiographic Exam *PLAX M-Mode Full Screen*

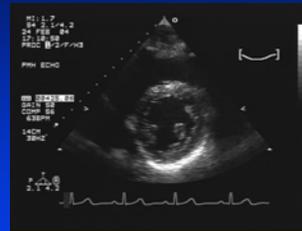
- Next switch to full-screen M-mode imaging. Record 10 beats of full screen M-mode.
- Record two 5 second freeze-frame images
- Without a change in position, switch back to 2-D and record for 10 additional beats



To Proceed
Press Enter

AASK Echocardiographic Exam *Parasternal Short Axis*

- Record 10 beats at quiet respiration in PSAX view
- Important to obtain as circular an image as possible at the level of the papillary muscles (not mitral leaflets)
- Use lateral gain as necessary so that myocardial borders can be identified

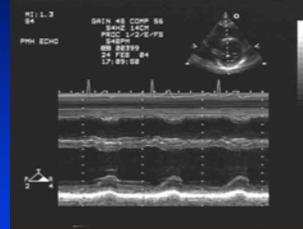


To Proceed
Press Enter

Record 10 beats at quiet respiration in the parasternal short axis view. When imaging in the PSAX, it is crucially important to obtain as circular an image as possible, directing the transducer away from the mitral valve (towards the feet) where the mitral valve motion is lost or where there is only minimal excursion of the leaflets. PSAX views, which appear elliptical or egg-shaped, indicate that the echo sector has intersected the LV in an oblique fashion instead of perpendicular to the long-axis. Use of M-mode measurements from such oblique echo images result in large overestimation of LV mass.

AASK Echocardiographic Exam *M-mode PSAX*

- Position M-mode cursor perpendicularly through LV cavity just below tips of mitral leaflets
- Display 2-D update image on screen with M-mode recording, at 50mm/s
- Record 10 beats during quiet respiration

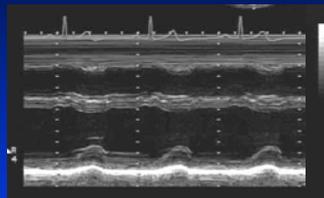


To Proceed
Press Enter

The M-mode cursor should then be positioned perpendicularly through the ventricular septum, LV cavity and LV posterior wall at or just below the mitral leaflet tips. The technologist should display the 2-D update image on the screen with the M-mode recording of the LV at 50 mm/sec (with 10 beats recorded during quiet respiration). Subsequently the technologist should record 10 beats of the full-screen M-mode echocardiogram of the LV at 50 mm/sec during quiet respiration. The technologist should record two 5 second freeze-frames of this full-screen M-mode image of the LV at gently held expiration. Without change in transducer position, switch back to 2-D and record for 10 additional beats.

AASK Echocardiographic Exam *M-mode PSAX Full-Screen*

- Switch to full-screen M-mode and record 10 beats at 50 mm/s during quiet respiration
- Record two 5-second freeze-frames of this full-screen image at gently held expiration
- Without change in transducer position, switch back to 2-D and record for 10 additional beats

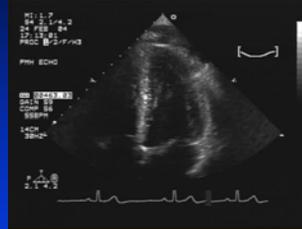


To Proceed
Press Enter

Subsequently the technologist should record 10 beats of the full-screen M-mode echocardiogram of the LV at 50 mm/sec during quiet respiration. The technologist should record two 5 second freeze-frames of this full-screen M-mode image of the LV at gently held expiration. Without change in transducer position, switch back to 2-D and record for 10 additional beats.

AASK Echocardiographic Exam *Apical four-chamber*

- Record 10 beats of the LV in the apical four-chamber view. If possible, use same depth setting used in obtaining PSAX image
- Next freeze image in end-diastole and measure long-axis of LV from the apex to the middle mitral valve plane and record for 5-seconds.

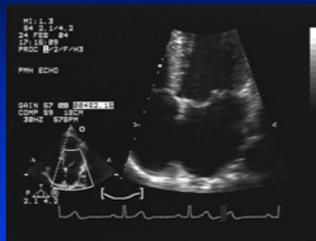


To Proceed
Press Enter

The 2-D method of calculating LV mass in the AASK Study will be the area length method. It requires endocardial and epicardial tracing of the left ventricle in the short axis view, and measurement of diastolic long-axis of the LV in the apical 4-chamber view. The technologist should make every attempt to display the true long axis of the LV, avoiding “foreshortening” of the chamber and possible error in subsequent calculation of mass. Measurement of the length of the LV will be made from the apex to the middle mitral valve plane from still frames of apical 4 chamber view in end-diastole (simultaneous with onset of QRS complex on ECG). If possible, the view used to measure the LV length should be at the same depth setting as the short axis view to minimize need for adjusting the image scale from a short axis view to a long axis view during the area/length measurements.

AASK Echocardiographic Exam *Left Atrial Area*

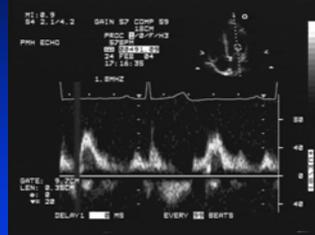
- Zoom on left atrium in apical 4-chamber
- Record 10 beats of the left atrium in quiet respiration
- Next record a five-second freeze frame of the left atrium in end-systole



To Proceed
Press Enter

AASK Echocardiographic Exam LV inflow Doppler

- In the apical four-chamber view, position pulsed wave sample volume at tips of mitral leaflets during diastole
- Sample volume 1 to 2 mm
- Record transmitral flow velocity with 2-D update image displayed on screen for 10 beats, at 100 mm/sec.

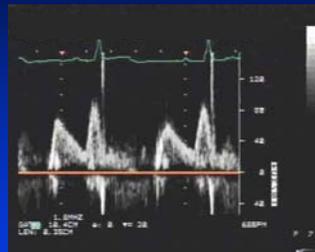


To Proceed
Press Enter

Pulsed Doppler recording of transmitral flow velocity should be performed from the apical four-chamber view using the 2.5 MHz transducer with the sample volume (1-2 mm) positioned parallel to the presumed direction of inflow at the tips of the mitral leaflets during diastole. An attempt should be made to record beats demonstrating the highest peak velocities and narrowest spectral dispersion. The technologist should display the 2-dimensional update image on the screen with the Doppler recording of transmitral flow velocity recorded at 100 mm/sec (with 10 beats recorded during quiet respiration).

AASK Echocardiographic Exam LV inflow Doppler full screen

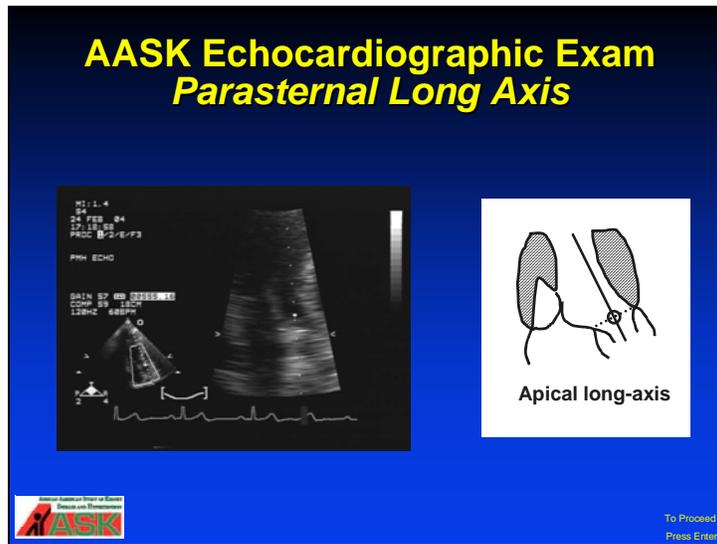
- Switch to full-screen Doppler
- Record 10 seconds of full-screen Doppler during quiet respiration
- Record two 5-second full-screen Doppler images at gently held expiration.



To Proceed
Press Enter

Subsequently the technologist should record ten beats of the full-screen Doppler transmitral flow velocity during quiet respiration. Finally the technologist should record the full-screen Doppler image of transmitral flow velocity at held expiration, two different freeze-frame samples for 5 seconds each.

AASK Echocardiographic Exam Parasternal Long Axis



This image demonstrates the proper position for the sample volume and the corresponding Doppler flow velocity spectral envelope recorded in the LVOT tract from the apical long-axis view. The sample volume should be placed approximately 0.5 cm proximal to the aortic annulus, and adjusted so that the maximum velocity with a clear envelope obtained. This recording can be used to estimate stroke volume and linear cardiac output. Record 5 beats demonstrating sample volume position.

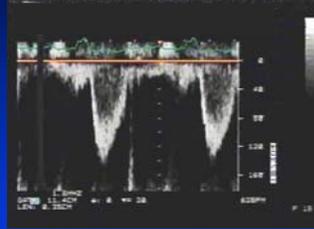
AASK Echocardiographic Exam Parasternal Long Axis

- Next display pulsed wave Doppler velocities of the LVOT with the 2-D update image on the screen.
- Record 10 beats during quiet respiration at speed of 100mm/s.

The technologist should display the 2-D image on the screen with the Doppler recording at 100 mm/sec of LVOT velocity. Record 10 beats during quiet respiration.

AASK Echocardiographic Exam LVOT Velocity Full Screen

- Next record for 10 beats a full-screen Doppler recording of LVOT velocity during quiet respiration
- Finally record for two 5 second periods in freeze-frame mode two separate Doppler recordings of LVOT velocity

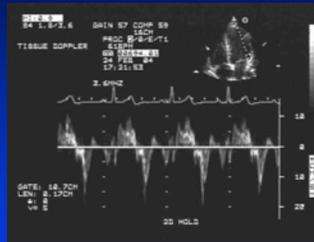


To Proceed
Press Enter

Finally the technologist should record for two 5 second periods in freeze frame mode a full-screen Doppler recording of LVOT velocity during quiet respiration.

AASK Echocardiographic Exam Tissue Doppler Imaging

- Pulsed Tissue Doppler recordings should be obtained by placing sample volume at lateral part of the mitral valve annulus, from the apical 4-chamber view
- Use predetermined settings for TDI if available
- If presets not available, decrease PW Doppler gain (-15 to 20 Db), use velocity filters to obtain low-frequency signals (5-20 cm/s), and scale to include systolic and diastolic velocities (± 15 -20 cm/s)
- Display 2-D update image on screen and record for 10 beats at 50-100 mm/s (depending in part on HR)



To Proceed
Press Enter

Pulsed Tissue Doppler recordings should be obtained by placing Doppler sample volume at the lateral base of the LV (lateral part of the mitral valve annulus), performed from the apical four-chamber view. An attempt should be made to record beats demonstrating the highest peak velocities and narrowest spectral dispersion. The technologist should display the 2-D update image on the screen with the Doppler recording of myocardial tissue velocity recorded at 50-100 mm/sec (with 10 beats recorded during quiet respiration). Subsequently the technologist should record ten beats of the full-screen Doppler myocardial tissue velocity during quiet respiration. Finally the technologist should record, for 5 seconds in freeze-frame mode, the full-screen Doppler image of myocardial tissue velocity at held expiration. Successful TDI will be demonstrated by obtaining characteristic wave pattern of myocardial tissue velocities: forward systolic wave, an early diastolic myocardial velocity and an atrial contraction signal.

Blood pressure recording

- Blood pressure will be obtained by the technician at the end of the study while the patient is in the supine position.
- It will be recorded on the echocardiographic technologist's worksheet (form 1117; figure X)
- Blood pressure is an essential part of the echocardiographic outcome measurements



To Proceed
Press Enter

The AASK Cohort Study Coordinator at each clinical center is responsible for providing any revisions of Form 117 to their echocardiographic technician.

Review of Study

- Scan study to assess for adequacy and completeness
- Measure and record on data transmission sheet (appendix B) M-mode septal wall thickness, posterior wall thickness, and LV diastolic cavity dimension
- Measure and record LVOT flow velocity integral
- Measure and record E max and A max from the LV inflow recording
- Document a self-report quality score (good, fair, poor, not obtained) for M-mode, 2-D and Doppler portions of the exam.



To Proceed
Press Enter

At the completion of the study, the technologist will briefly scan the tape/optical disk for adequacy and completeness of study. Additionally, from one portion of the M-mode recording the technologist will measure (one beat only) septal wall thickness, posterior wall thickness, and LV diastolic cavity dimension. These values will be recorded on the data transmission sheet (Appendix B) sent from the field center echo lab to the ERC. A self-report quality score (good, fair, poor, not obtained) for M-mode, 2-D and Doppler portions of the exam will also be recorded on the preliminary interpretation sheet. From the LV outflow recording, measure one flow velocity integral. From the LV inflow recording, measure one E max and A max.

Echo “alert” parameters

- Severe aortic stenosis
- Aortic dissection
- Vegetation
- Tumor
- Cardiac Tamponade
- LV thrombus



To Proceed
Press Enter

“Alert” findings are those echocardiographic conditions, which will trigger an “urgent” phone call from the echocardiography Center to the AASK study coordinator at the local site. Notify the local AASK PI if any of these alert findings are present. The AASK study coordinator and/or PI will then be responsible for calling the patient’s referring physician (or physician or record) on an “urgent” basis. Field center echocardiography technologists will enter any of the “alert” findings listed below, which they identify during the examination on the Echocardiographic Technologist’s Worksheet (Appendix B). Cardiac tamponade will be defined as the presence of pericardial effusion with RA and RV chamber collapse and respiratory variations exceeding 30% in Doppler peak velocities recorded at any cardiac valve site.

Data Transmission

- Record approximately six studies per super VHS tape, or 10 studies per CD or optical disk
- Copy tape and/or disk prior to shipping and store in secure place
- Copy Echocardiographic Technologist's Worksheet (appendix B) and place one copy in patient's record at Field Center and include second copy in shipment with corresponding VHS/disk
- Package VHS tapes securely to prevent damage
- Include in shipment copy of log listing videotapes/disks sent by number



To Proceed
Press Enter

Field Center technologists will record their studies on super VHS tape, approximately six studies per 60-minute tape, and/or on a CD or optical disk, approximately 10 studies per disk and send them to the Echocardiography Core Lab. The technologists will produce duplicate copies of the Echocardiographic Technologist's Worksheet (appendix B) – one copy to stay in the patient's record at the Field Center and the second copy to be sent to the Echocardiography Core Lab along with the videotape. Field Center technologists will make a copy of the tape and/or disk prior to shipping and store in a secure place. Field Centers will package their super-VHS videotapes securely, using sufficient packing material to prevent damage to tape casements during shipment. A copy of the log listing the videotapes sent by number should accompany the videotapes/disks.

Shipments will be sent via Federal Express. The tapes will be sent to:

Katharine Lymberis
Attn: the AASK Cohort Study
Echocardiography Core Laboratory
Cardiovascular Research Foundation
55 East 59th Street
6th Floor
New York, NY 10022
Telephone: 212-851-9193
Fax: 212-851-9330
e-mail: KLymberis@crf.org

**Questions Contact for Echo
Technical Questions:**

Core Lab Staff
AASK Echocardiography
Gail Peterson, MD

Sonographer
Cindy Todd, RDCS
(email ctodd@parknet.pmh.org)

Phone: 214-645-7500
Fax: 214-645-7501



To Proceed
Press Enter

11.5 References

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2. Amann K, Breitbach M, Ritz E, Mall G: Myocyte/capillary mismatch in the heart of uremic patients. *J Am Soc Nephrol* 9:1018-1022, 1998
3. Casale PN, Devereux RB, Milner M, Zullo G, Harshfield GA, Pickering TG, Laragh JH: Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. *Ann Intern Med* 105:173-178, 1986
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5. Bikkina M, Larson MG, Levy D: Asymptomatic ventricular arrhythmias and mortality risk in subjects with left ventricular hypertrophy. *J Am Coll Cardiol* 22:1111-1116, 1993
6. Cooper RS, Simmons BE, Castaner A, Santhanam V, Ghali J, Mar M: Left ventricular hypertrophy is associated with worse survival independent of ventricular function and number of coronary arteries severely narrowed. *Am J Cardiol* 65:441-445, 1990

7. Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS: The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. *Ann Intern Med* 117:831-836, 1992
8. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, Reboldi G, Porcellati C: Prognostic significance of serial changes in left ventricular mass in essential hypertension. *Circulation* 97:48-54, 1998
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1. De Simone G, McClelland R, Gottdiener JS, Celentano A, Kronmal RA, Gardin JM: Relation of hemodynamics and risk factors to ventricular-vascular interactions in the elderly: the Cardiovascular Health Study. *J Hypertens* 19:1893-1903, 2001
2. Gardin JM, McClelland R, Kitzman D, Lima JA, Bommer W, Klopfenstein HS, Wong ND, Smith VE, Gottdiener J: M-mode echocardiographic predictors of six-to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study). *Am J Cardiol* 87:1051-1057, 2001

11.6 Appendices

Appendix A: Form 117 (Echo Mailing and Echo Local Results Form) or “Data Transmission Sheet”

Appendix B: AASK Cohort 10-Step Echo Scanning Protocol

Appendix C: AASK Cohort Echo Study Log

Appendix D: Normal Ranges

Appendix A:

**Echo Mailing Form and Echo Local Results Form
(referred to in these slides as the “Data Transmission Sheet”)**

The AASK Cohort Study Coordinator at each clinical center is responsible for providing any revisions of Form 117 to their echocardiographic technician.

Appendix B: AASK COHORT Echo Scanning Protocol

1. ___ ECG signal is visible at bottom of screen
2. ___ Record M-mode at 50 mm/sec and ___ Doppler at 100 mm/sec
3. ___ Aorta and left atrium*
 - . ___ record 10 beats of the 2-D Parasternal Long Axis view focusing on the Ao and LA
 - . ___ freeze the 2-D image in systole and measure the aortic annulus
 - . ___ record 10 beats of continuous M-Mode of the LA and Ao
 - . ___ record 10 beats of the 2-D short axis view of the Ao and LA
4. ___ Parasternal long-axis view of LV: record for 10 2-D beats*
5. ___ 2-D guided parasternal long-axis M-mode of LV*
 - . ___ record 10 beats with 2-D update; then without change in transducer position:
 - . ___ record 10 beats of the full-screen M-Mode
 - . ___ record for 5 seconds in freeze-frame mode of the 2-D directed M-mode
 - . ___ record again for 5 seconds in freeze-frame mode the 2-D directed M-mode
 - . ___ without change in transducer position switch to 2-D and record for 10 beats
6. ___ Parasternal short-axis view of LV mid-cavity; record 10 2-D beats*
7. ___ 2-D guided parasternal short-axis M-mode of LV*
 - . ___ record 10 beats with 2-D update then without change in transducer position:
 - . ___ record 10 beats of the full-screen M-Mode
 - . ___ record for 5 seconds in freeze-frame mode of the 2-D directed M-mode
 - . ___ record again for 5 seconds in freeze-frame mode the 2-D directed M-mod
 - . ___ without change in transducer position switch to 2-D and record for 10 beats
8. ___ Apical Four-Chamber View*
 - . Pulsed Doppler at mitral leaflet tips
 - . ___ record 10 beats of 2-D update
 - . ___ record 10 beats of Doppler with 2-D update
 - . ___ record 10 beats of full-screen Doppler: at 100mm/sec at held-expiration
 - . ___ record for 5 seconds in freeze-frame mode the full-screen Doppler transmitral flow velocity
 - . Pulsed Doppler in LV outflow tract (5 mm proximal to aortic valve)
 - . ___ record 10 beats of 2-D update
 - . ___ record 10 beats of Doppler with 2-D update
 - . ___ record 10 beats of full-screen Doppler at 100 mm/sec at held-expiration
 - . ___ record for 5 seconds in freeze-frame mode the full-screen Doppler LV outflow velocity
 - . ___ Record early and late myocardial velocity with pulsed tissue Doppler imaging at base of lateral wall
 - . ___ Record 2-D image of LA for area measurement
 - . ___ Measure the length of ventricle from the apex to the middle mitral valve plane
9. ___ Blood Pressure taken in supine position and recorded on Worksheet

*10 beats for tapes. 3 to 5 beats for digital

Appendix C:
AASK Cohort Echo Study Log
(send with tape/optical disk to CRF)

Site Name _____

Site Number _____

AASK Name	AASK Number	Date (mm/dd/yyyy)	Study Year (1,3,5)	AASK Tape #	Counter #	AASK Optical Disk #	Blood Pressure ___/___

Appendix D:
Normal Ranges

	Normal Range
2-D	
aortic annulus:	1.8-2.4 cm
IVSd	0.6-1.1 cm
LVPWd	0.6-1.1 cm
LVIDd	3.6-5.2 cm
LVIDs	2.1-4 cm
LA area 4-ch	12.5-15.5 cm ²
M-Mode	
Aortic root	2-3.7 cm
LA	1.9-4 cm
IVSd	0.6-1.1 cm
LVPWd	0.7-1.1 cm
LVIDd	3.7-5.6 cm
LVIDs	2-3.8 cm
Doppler	
LVOT TVI	18-22 cm
Mitral peak E wave	70-100 cm/sec
Mitral peak A wave	45-70 cm/sec
Mitral E wave deceleration time	160-220 msec
Tissue Doppler	
Em	13-21 cm/sec
Am	7-12 cm/sec
Sm	9-13 cm/sec

CHAPTER 12. MEASURING ECHOCARDIOGRAMS AT THE CVD CORE LABORATORY AND TRANSMITTING DATA TO THE DCC

12.1 Data Transmission

Field Center technologists will record their studies on super VHS tape, approximately six studies per 60-minute tape, and/or on a CD or optical disk, approximately 10 studies per disk, and send them to the Echocardiography Core Lab. The technologists will produce duplicate copies of Form 117 (Appendix A of Chapter 11) - one copy to stay in the patient's record at the Field Center and the second copy to be sent to the Echocardiography Core Lab along with the videotape.

Field Center technologists will make a copy of the tape and/or disk prior to shipping and store in a secure place.

12.2 Packing and Shipping

Field Centers will package their super—VHS videotapes securely, using sufficient packing material to prevent damage to tape casements during shipment. Shipments will be sent via Federal Express. Note: Phone number will be included with address in case of misrouted shipment. The outside of each package should bear the Field Center's return address, sender's name and phone number.

The tapes/optical disks will be sent to:

**Katharine Lymberis
Attn: the AASK Cohort Study
Echocardiography Core Laboratory
Cardiovascular Research Foundation
55 East 59th Street
6th Floor
New York, NY 10022
Telephone: 212-851-9193
Fax: 212-851-9330
e-mail: KLymberis@crf.org**

These videotapes/disks should be accompanied by a copy of the log listing the videotapes sent by number.

Ms. Roca will record receipt of the imaging media (VHS tape, CD or MO) with accompanying Form 117 (Appendix A of Chapter 11) into the dedicated database and log sheets, which will contain the imaging media number, field

site and date of receipt. The videotape and enclosed field center subject identification sheets will be transferred to the reading laboratory.

Notification of tape imaging media receipt (VHS tape, CD or MO) will be transmitted within 24 hours to the field center and the Data Coordinating Center (Cleveland Clinic) via E-mail or FAX.

12.3 Database Entry of Imaging Media I.D. Numbers

- In the Echocardiography Core Laboratory (ECL) information from the field center Echocardiographic Technologist's Worksheet containing subject's I.D. is entered by the data manager into a specially configured database maintained on both hard-disk of dedicated PC and on-line server (as a back-up).
- Linkage of this database with that at the Data Coordinating Center via I.D.numbers will facilitate use should partial re-reads be required for potential future substudies. Data entry will include study name, imaging media code (VHS tape, CD or MO) and a number, field site, patients I.D. number and name code, echo acquisition date and the date when echo is received by ECL.
- The six digit subject's I.D. number is assigned by the Data Coordinating Center at Cleveland Clinic and it will be verified using the digit verification program, so incorrect I.D. entries can be identified and corrected.

12.4 Echocardiographic Core Lab Reading Procedure

- Measurements will be made by assigned Echocardiography Core Lab readers (cardiovascular specialists with expertise in Adult Echocardiography; they will have assigned ERL Reader I.D.) using a computerized review station (DigiView, Release 3.0; Digisonics, Houston, TX).
- Imaging media will be scanned by ECL readers to identify appropriate segments of 2-D and 2-D guided M-Mode recordings of LV, Aortic root, Left atrium, LV outflow PW Doppler and mitral annulus myocardial tissue PW Doppler for digitization (for VHS tapes), measurements, calculations and storage. Three beats of each parameter will be measured and averaged.
- Participant's blood pressure will be entered from Echocardiographic Technologist's Worksheet and used in a calculation of left ventricular end-systolic wall stress (ESWS); heart rate will be obtained from successive RR intervals of the LV M-Mode recording and that value will be applied to all heart rate based calculations (Stroke volume, Cardiac Output, Cardiac Index).

Following each measurement sequence, data are temporarily saved to hard disk. After completing a report and before closing the study, all the measurements and calculations will be automatically exported as an ASCII text file format. After daily reading session is over, digitized images and quantitative measurements and calculations will be transferred from PC hard disk and stored both to 650 MB optical disk and dedicated network database. Weekly, ASCII data will be transferred via Internet connection to Data Coordinating Center from ECL.

The completed VHS tapes and/or CD or MO will be stored, in numerical order, in special locked cabinets in the reading laboratory.

12.5 Echocardiography Measurements and Assessments in AASK Echo Substudy

Following quantitative measurement and calculations utilizing Digisonics digital image management system will be obtained:

M-Mode:

Intraventricular septal thickness in diastole (IVSd)
Left ventricular posterior wall thickness in diastole (LVPWd)
Left ventricular internal dimension in diastole (LVIDd)
Left ventricular internal dimension in systole (LVIDs)
Left atrial dimension (LA)
Aortic root dimension (Ao)
Left ventricular percentage of fractional shortening (LVFS, calculated)
Left ventricular ejection fraction (LVEF, calculated)
Left ventricular end systolic stress (LVESs, calculated)
Left ventricular mass (LVMass, calculated)

2-D ECHO:

Intraventricular septal thickness in diastole (IVSd)
Left ventricular posterior wall thickness in diastole (LVPWd)
Left ventricular internal dimension in diastole (LVIDd)
Left ventricular internal dimension in systole (LVIDs)
Left atrial area (LAa)
Aortic root dimension (Ao)

Left ventricular mass (LV Mass, Area-length method, calculated)

Spectral Doppler:

Left ventricular outflow tract systolic velocity integral (LV TVI)

Mitral inflow peak early velocity (E)

Mitral inflow peak late velocity (A)

E/A ratio

Early diastolic myocardial velocity at lateral annulus (Tissue Doppler Imaging, Em)

Late diastolic myocardial velocity at lateral annulus (Tissue Doppler Imaging, Am)

Stroke volume (SV), cardiac output and left ventricular end-systolic wall stress (ESWS)

will be calculated combining parameters obtained from 2-D, Spectral Doppler and measured heart rate using DigiView software with incorporated formulas.

($SV = 2D \text{ Ao area} \times LVOT \text{ TVI}$; $CO = SV \times HR$).

Calculated parameters indexed for patient's weight and height will be computed at Data Coordinating Center (Cleveland Clinic) since they have those demographic data and will be following:

Left ventricular mass / height (LV Mass/Ht)

Left ventricular mass / height^{2.7} (LV Mass/Ht^{2.7})

Left ventricular mass index (LV MassIx; g/m²)

Left ventricular Cardiac Index (LV CI; L/m/m²).

12.6 Measurement Conventions: 2-D Mode and 2-D Derived M-Mode:

12.6.1 Selection of Beats for LV Measurements:

Parasternal short axis view of the LV where the M-Mode cursor traverses the center of a circular cross-sectional image at or just below the tips of the mitral leaflets will be utilized. Proper cephalad-caudad orientation of the sector will be identified by minimal motion of mitral valve structures (presumably distal mitral tips or chordae tendinae), and absence of structures consistent with the

bases of the papillary muscles. Cross sectional images where the estimated eccentricity (ratio of vertical midsectional chord to horizontal midsectional chord) of greater than 1.1 will be excluded from analysis. Attempts will be made to select beats with optimal definition of the posterior wall epicardial-pericardial interface, defined by visual extension into diastole of the anterior aspect of the small systolic posterior free space. Care will be taken to exclude right ventricular muscular structures (e.g., moderator band, crista supraventricularis) from the right ventricular aspect of the septum by selecting beats where these structures do not abut against the septum within the path of the M-Mode cursor.

12.6.2 Selection of beats for Left Atrial and Aortic Root Measurements

M-mode recordings where the cursor intersects the left atrium at its most posterior displacement will be utilized for measurement. Care will be taken to avoid misinterpretation of the true posterior left atrial border by confounding of the interface by pulmonary veins, side lobe artifact, or tangential direction of the cursor.

12.6.3 M-Mode Measurements

American Society of Echocardiography (ASE) criteria will be used (Figure 1). Structures are identified from leading edge to leading edge; LV measurements are made in tandem at the onset of the QRS complex; the aortic root is measured at the onset of the QRS; the left atrial dimension is measured at the peak anterior excursion of the atrial-posterior interface at the end-systole.

12.6.4 Doppler Measurements

Left ventricular inflow and outflow pulse-wave Doppler “best beats” characterized by minimal spectral dispersion and maximal velocity will be selected. Utilizing the Digisonics system ability, the LV (aortic) outflow systolic velocity integral (LV TVI) will be contoured from the outer edge of the spectral recording, i.e., using maximum rather than modal frequency shifts.

The mitral peak E and A velocities, as well as early and late myocardial tissue velocity (Em and Am) will be identified and entered by trackball at the maximum excursions of the spectral profile.

12.7 Offline Image Analysis System

The system utilized for AASK Echo Substudy is the computerized review station (Digiview, Release 3.0; Digisonics, Houston, TX) equipped with digitizing tablet and monitor screen overlay. System specifications are provided in Appendix D. DigiView echocardiography workstations provide general image management together with integrated reporting. DigiView systems work

with either video or digital data, are DICOM compliant, and can be configured as capture, review, or full systems. Images can be read from or stored to devices connected to the workstation (VHS, CD, MO, floppy, Jaz drive or network server).

The software quantitation package is available for performing 2-D, Doppler, and M-mode measurements on or off-line. Measurements may be performed on-screen from either video or digital images (CD or optical disk).

12.8 Appendices

Appendix A: DigiView image management system specifications

Appendix A

DigiView™

System Specifications

Image Capture from Video

Black & White and Color

Resolution: 640x480x16-bit color depth

30 frames per sec, 60 fields per sec.

Video source: ultrasound video output or videotape, SVHS or composite, NTSC or PAL

User defined capture controls: no. of cycles per capture, no. of frames per cycle, prospective or retrospective, stages, views, triggered or manual (depending on configuration ordered).

Triggering: ECG signal on tape or online, manual, R to R for single or multiple cycles.

Direct Reading of Digital Images

Acuson - Sequoia or Aspen

HP Sonos TIFF image files

DigiView native format

All standard DICOM files

Media or network (DigiView native)

DICOM network pending

Display

VCR type display controls

Video or digital images

Full, dual, or quad screens

Preview screen for showing all study sequences

Multiple cycles, cineloops, or still frames

Resolution: 1024x768x16-bit color depth

Graphics overlay capability

Optional flat screen (active matrix LCD)

Integrated Reports

User configurable report formats

Custom clinical comments

Custom normal range tables

Links to ultrasound systems for uploading patient demographic and measurement information.

Measurement and Analysis

Incorporates all ASE recommendations.

User selectable or preset view protocols.

Uploading of measurements from ultrasound system, entry via keyboard, or calculation using graphics overlay on video or digital images.

Stress Acquisition and Analysis (optional)

User defined protocols

High heart rate triggering

Clinical compression or pseudo digital VCR

Stress exam documentation, wall motion scoring, calculations package, and stress report.

System Components

Pentium 400 MHz CPU, 9 GB SCSI hard drive, 256 MB memory, floppy disk, CD.

Monitor, printer, VCR, optical disk drive per configuration selected.

Windows 95, or NT

Network ready

Storage Options

Supported formats: DICOM, TIFF, JPEG, BMP, AVI, and others.

Uncompressed or compressed, with user specified compression factor.

Supported storage devices: Hard drive, floppy drive, CD, optical disk (5 1/4 and 3 1/2), jaz cartridge, network file server.

Optical Jukebox (130 GB storage)

Database

Access database for image index tables

Integrated image and report databases

Up to 96 multi-cycle image sequences per study, (2 GByte image capacity per study, expandable with additional memory)

Local or remote (file server) database

Communications Options

Fax reports direct from application

E-mail reports & images direct from application

System Configuration Options

DigiView Full, Capture, and Reading

DigiView Stress Acquisition and Review

Physical Specifications (Computer)

Dimensions: 6.5"W x 17.5"H x 17.5"D

Weight: 30 lbs.

Power Requirements: 115/230 Volts

6.2/3.5 Amps

60/50 Hz

CHAPTER 13. AMBULATORY BLOOD PRESSURE MONITORING

13.0 Introduction

Twenty-four-hour Ambulatory Blood Pressure Monitoring (ABPM) will be performed at visits C0, C24 and C48. The monitor will record blood pressure every 30 minutes. A Blood Pressure Measurement Form 110 should be completed on the same day that the ABPM is placed.

13.1 Equipment

13.1.1 Software

Install ABP software on an IBM PC or compatible computer.

13.1.2 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

13.1.3 Monitor Cable

The monitor cable is attached to a serial port on the PC. The other end of the cable attaches to the monitor arrow to arrow.

13.1.4 Cuffs

Tru-Cuff (SpaceLabs) are reusable, single hose, and can be self applied.

Cuff sizes are as follows:

- small adult 17-26 cm
- standard adult 24-32 cm (if arm circumference is between 32 and 33, use large adult cuff)
- 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. Refer to the diagram on the cuff that indicates left or right arm. This diagram will show where the hose should exit. 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.

13.2 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 about one hour. Ask the participant to wear a short-sleeved shirt or blouse, or a garment with loose sleeves, to accommodate placement of the cuff.

13.3 Programming/“Initializing” the ABP Monitor

The AASK 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. Make sure default settings are set for AASK. To check, chose “Setup” from the menu bar. Then Choose “Monitor” from the pull down menu. Make sure that the default setting is AASK. If not, change the default setting to AASK.
6. From the menu bar click on “Communications.” From the “Communications,” choose “INIT monitor.” Make sure the load settings say AASK and that the settings are as in Table 1 (this should be the default that you have defined in “Set-Up, Monitor Initialization).
7. If you know who will be wearing the monitor, enter the subject’s name AASK ID in the “Patient Name” field followed by “a” if this is the baseline visit (C0), “b” is this is the second year (C24), and “c” if this is the fourth year (C48). 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 AASK identifier is JENAL, enter JENALa1 for the first year, first attempt).
8. If a second attempt is required, obtain within the window. If the second attempt is unsuccessful, send 1 and 2 to the Core laboratory.

9. In the "Patient ID Number" field, enter the patient's 6 digit AASK number field followed by "a" if this is the baseline visit (C0), "b" if this is the second year (C24) and "c" if this is the fourth year (C48). 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 AASK identifier is 110027, enter 110027a1 for the first year, first attempt). 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 AASK ID and number when you download later.
10. Click on "Start Init" to initialize the monitor. Follow the screens and initialize the monitor with "Monitor Connected Directly". Disconnect monitor from cable, turn it off, and place monitor in its padded carrying case.
11. Fill out the top section of the AASK ABPM Initialization and Placement Form (Form 170). 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: AASK

- 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

13.4 Placement of the BP Monitor on the Participant

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). The cuff selected depends on the patient's arm circumference *Record which arm you used on the ABPM Initialization and Placement Form 170. 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 an aneroid BP measurement, 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.

13.5 ABPM BP Calibration Verification Readings

Verification readings will be performed. The first 5 BP readings on the monitor are “unblinded” for this purpose.

- 3 readings using the patient’s right arm and using the Tycos Classic Hand aneroid sphygmomanometer will be obtained and recorded on Form 110 (Blood Pressure Measurement Form) followed by three readings using the patient’s non-dominant arm and using the SpaceLab ABPM.
 - Record both the aneroid and ABPM readings on Form 110 and Form 170.
- If the three ABPM blood pressure readings do not indicate an “error” signal on the display, the unit has been successfully placed. Manually abort the 4th and 5th ABPM readings by pressing the blue button once to start and once to stop (do this two times). This is done to prevent the participant from seeing their BP (the monitor displays BP for the first five readings only).

IMPORTANT:

- Record the time that the ABPM was placed on the participant. Note that the ABPM may have been initialized prior to placement. (Note: Use 24-hour clock. Noon = 12:00 pm.) The serial number and the arm upon which the monitor was placed is also documented.
- Give the participant the Instructions to Participants (Appendix A). Review these instructions verbally. The participant is then ready to leave the clinic. Complete the remaining fields on the AASK ABPM Initialization and Placement Form 170 (Appendix B).

13.6 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 Initialization and Placement Form 170 for time placed]. Obtain at least 14 readings between 6 and 0 hours and 6 readings between 0 and 6 hours. If the required readings were not recorded, repeat the ABPM. If the participant has only worn it for <24 hours, ask the participant to wait a short time until a 24-hour recording has been obtained. A 23 to 25 hour recording is required. You may then remove the cuff from the subject's arm

and take the cuff and monitor to the ABPM computer. Enter the participant's AASK ID number and namecode on the top of Form 171.

13.6.1 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 identification number. Enter the patients AASK number followed by 3 zeros. For example, if the patient's AASK ID is 110027, enter 110027000. This number is not entered on Form 171. When "Select A Group" message box appears, select AASK from the scan groups. Click OK.
2. The screen will display the subject's AASK ID (this may be 9999 if that's how the monitor was initialized) and identification number, which is the patient's ID number followed by 3 zeros.
3. If initialized with 9999, change the name field to the AASK Namecode--followed by "a" if this is the baseline visit (C0), "b" if this is the second year (C24) and "c" if this is the fourth year (C48). 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 # JENAL for his first year ABPM recording would be JENALa1.* This is entered on Form 171 question 7 but also include the ID number prior to the Namecode (110027JENALa1). 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 6 acceptable readings between 0 and 6 (12:00 midnight to 6:00 AM) and 14 acceptable readings between 6 and 0 (6:00 AM and 12:00 midnight). If so, the monitor is acceptable. If fewer readings were obtained, 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 AASK ABPM Downloading, Copy Scan and Mailing Form (Form 171).
6. Irrespective of whether there were adequate number of readings, copy the scan to a Floppy Disk (Appendix D)
7. Print out a hard copy of the recording and place in patient's chart. Also, be sure to include a hard copy printout along with the disk and the completed Form 171.
8. To initialize the monitor for the next subject, repeat steps in "Programming/ Initializing" the ABP Monitor. Remember to discard alkaline batteries and replace with new batteries prior to the next initialization.

13.6.2 Procedure for Copying Scan to a Floppy Disk

1. Complete Floppy Disk Label with Patient's ID, Monitor year (e.g. C0, C24, or C48) and date the recordings were started.

2. Go to File Menu and Select Copy Scan
3. Select Button under From Group and Select AASK
4. Select Button under To Group, Go to triangle and select ABP (Drive A).
5. Select subjects file (e.g. *JENALa1*).
6. Under Select Directory, choose Working
7. Select OK
8. Confirm Scan to be copied and Select YES
9. Make a second copy to keep at your site
10. Place the Floppy Disk in a Mailer with a copy of Form 171 and a paper copy of the ABPM in case there is a problem with the floppy disk and send by Fed Ex to:
Katharine Lymberis, Attn: The AASK Trial, Ambulatory Blood Pressure Monitoring Core Laboratory, Cardiovascular Research Foundation, 55 East 59th Street, 6th Floor, New York, NY 10022 (Appendix H).

Complete the bottom section of the AASK ABPM Downloading, Copy Scan and Mailing Form 171. **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 before the first patient.**

13.7 Maintenance of ABP Monitor

13.7.1 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 is 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 for each unit. Problems and solutions are also recorded. All maintenance logs should be stored in a permanent binder.

13.7.2 Comparison of ABP Monitor to Conventional Device

To check the calibration of the monitor, use the following procedure:

1. Obtain a full size mercury or aneroid 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 kept at your institution.
8. If a monitor has more than a three millimeters or 2% difference in the comparison, the monitor should be returned to Space Labs for calibration

13.7.3 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.

Cuff wraps with the bladder removed should be washed periodically. These can be washed on delicate cycle or soaked in mild detergent.

If the ABPM device needs serviced, SpaceLabs will charge a flat rate of \$425.00 per device if the device is sent to them and is not under warranty. Note: Centers have the option of purchasing a service contract for \$240.00 at the time the device is purchased. Each device has a 1-year warranty in which there will be no service charge if the device needs to be serviced within the 1-year time frame. Contact the SpaceLabs representative for further details.

13.7.4 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 SpaceLabs for repair. Record inspection results on internal form.

13.7.5 Calibration

The ABPM should be calibrated once each year for each ABPM device and documented/entered on Form 172.

APPENDIX A

CARDIOVASCULAR RESEARCH FOUNDATION ABPM CORE LABORATORY AT LENOX HILL HOSPITAL

AMBULATORY BLOOD PRESSURE MONITORING INSTRUCTIONS TO PARTICIPANTS

- This portion of the AASK study is very important because we believe that the blood pressure obtained by this procedure will better indicate the effect of blood pressure on kidney and heart disease.
- We believe that the blood pressure readings obtained during sleep may be the most important. So please make every effort to keep the monitor recording during sleep. It is important that the ABPM be worn for a full 24-hour period. If a full 24-hour period is not met, you may be asked to wear this ABPM again.
- Wear a shirt/blouse with a loose fitting sleeve on the day that the monitor is placed. The cuff and tubing will be placed directly on the arm, not over clothing.
- The monitor will take a reading every 30 minutes. It will beep to alert you when it is about to take a reading, countdown 5 seconds, and the measurement will take place. (Note: there will be no beep between midnight and 6 a.m.)
- When the cuff inflates, keep your arm relaxed, straight, and still.
- If possible, stop your activity and remain motionless during the reading. For example, if you are walking, stop temporarily.
- The monitor will not show the results of the blood pressure recording
- You can remove the monitor and cuff in order to shower. To do this, remove the monitor immediately after a measurement, shower, and be sure to put the monitor and cuff back on before the next reading (in 30 minutes).
- At night, place the monitor box to the side of your bed. If the noise of the monitor bothers you, place the monitor under a pillow.
- Please do not touch the buttons, remove the monitor box from its case, or turn it off, unless directed to do so.
- If the monitor is unable to take a reading, you will hear several short beeps. Check to be sure that:
 - 1) The arrow is placed directly over brachial artery (indicated by the ^ mark on your arm).
 - 2) The cuff is not too loose or too tight.
 - 3) The tubing is not kinked or disconnected.
 - 4) The cuff is at least one inch above the bend in your elbow

The monitor will try to take another reading in 2-3 minutes.

APPENDIX B
ABPM INITIALIZATION AND PLACEMENT INSTRUCTIONS TO FORM 170

Initialization and Placement of the monitor should follow the instructions in Sections 13.3 and 13.4 of this chapter of the Manual of Operations. Note: A Form 110 should be completed on the same day that the ABPM is placed.

Complete questions 1 through 4 on Form 170. Then,

5.
 - a. Enter Code Letter 'a' for C0 visit, code 'b' for C24 visit, and code 'c' for C48 visit.
 - b. Enter a code number of '1' for first attempt or '2' for second attempt.
6. Did the patient agree to wear an ABPM?
7.
 - a. Were new AA batteries put in before initializing the monitor
 - b. Certification ID of the staff person initializing the monitor (first letter of first name and first seven letters of the last name)
 - c. Is date and time correct on the device
8.
 - a. Arm used for cuff placement should be non-dominant arm unless no arm exists or there are medical reasons.
 - b. Arm circumference. If participants arm circumference is larger then 50cm, do not conduct ABPM on this participant. Form 170 will not be entered on this patient.
 - c. ABPM cuff size used
- 9.a.b.c. Record 1st, 2nd and 3rd aneroid readings. There must be 3 aneroid readings.
- d. Record the average systolic and diastolic readings. This is computer calculated.
- 10.a.b.c. Record the 1st, 2nd, and 3rd ABPM monitor readings. Manually abort the next two readings only if there were no errors with the first three readings. If there was an error, the 4th and 5th readings may be used.
- d. Record the computer calculated ABPM monitor average.
11. Were the last two readings manually aborted?
12. Date of placement after aneroid and ABPM readings are completed (mm/dd/yyyy).
13. Time of placement (24-hour clock).
14. Tech ID of person placing the ABPM device.
(first letter of first name and first seven letters of the last name)
15. Was a copy of the AASK ABPM instructions provided to the participant?
16. Were the AASK ABPM instructions reviewed with the participant?
17. Monitor serial number?

APPENDIX C

ABPM DOWNLOADING, COPY SCAN, AND MAILING INSTRUCTIONS TO FORM 171

Downloading, copy scan, and mailing of the ABPM should follow the instructions in Section 13.6 of this chapter of the Manual of Operations.

Complete questions 1 through 4 on Form 171. Note, the start date (Q4) must match the “date of placement” (Q12) on Form 170 or the database will not accept this form. Then,

5. Certification ID of the person reading the monitor.
(first letter of first name and first seven letters of the last name)
6. Date the monitor was downloaded (mm/dd/yyyy)
7. Enter the file name (AASK ID, Namecode) followed by the appropriate letter (a=Baseline (C0), b=First Follow-Up (C24), c=Second Follow-Up (C48)) that is followed by the appropriate number (1=first attempt, 2=second attempt). (See Section 13.6.1 of this chapter of the MOP.)
8. What time did the patient go to bed?
9. What time did the patient awaken in the morning (use 24-hour clock)?
10. Are there 6 or more acceptable readings between midnight and 6 a.m.?
11. Are there 14 or more acceptable readings between 6 a.m. and midnight?
Review the raw data for the 14 satisfactory BP readings during the day and 6 readings at night following the instructions in Section 13.6 of this chapter. If fewer than 14 readings during the day and 6 at night, reschedule the participant.
12. Was the ABPM data copied to a disk? (See Section 13.6.2 of this chapter of the MOP)
13. Certification ID of the person copying the ABPM data to disk
(first letter of first name and first seven letters of the last name)
14. Date the ABPM disk was mailed to the CV Core Lab (mm/dd/yyyy)? (See Section 13.6.2 of this chapter of the MOP). Be sure to include a hard copy printout along with the disk and the completed Form 171.

APPENDIX D

**CARDIOVASCULAR RESEARCH FOUNDATION
ABPM CORE LABORATORY AT LENOX HILL HOSPITAL**

FORM 170 AASK ABPM INITIALIZATION CHECKLIST

ID# _____

Date of Placement ___/___/_____

____ Tech ID: _____

Date: ___/___/_____*

____ New batteries installed

____ Monitor ID: _____

____ Initialized with

(a) dummy code (9999)

(b) AASK Name ID _____

(d) Time - time on desktop computer is correct (0=no, 1 = yes)

____ Monitor power off

FORM 171 AASK ABPM DOWNLOADING CHECKLIST

____ Tech ID: _____

Date: ___/___/_____

____ Download to computer

____ Full AASK ID entered (AASK number and three zeros)

____ File name: _____**

____ Review of raw data for 14 satisfactory BP readings 6-0 hours

____ Review of raw data for 6 satisfactory BP readings 0-6 hours

____ Reschedule participant if repeat session needed

FORM 171 AASK ABPM COPY SCAN CHECKLIST

____ Floppy Labeled Properly

Date: ___/___/_____

____ AASK ID: _____**

____ Copy Scan to Floppy Disk

____ Mail to CV Core

* Monitor should be placed within one week of initialization.

**File name = AASK Name ID = AASK Name ID, then "a" or "b" or "c," then "1" or "2"
(See MOP for detailed explanation.)

APPENDIX E

**CARDIOVASCULAR RESEARCH FOUNDATION
ABPM CORE LABORATORY AT
LENOX HILL HOSPITAL**

AASK ABPM CERTIFICATION WRITTEN TEST

1. On which arm should the ABPM be placed? R L Non-dominant

2. As part of AASK criteria, you should record 3 ABPM readings on the Initialization and Placement Form (Form 170). How many readings should you then abort before the patient leaves the office?
 - A. 3
 - B. 5
 - C. 2
 - D. You don't need to abort readingsWhy would you need to abort any readings? _____

3. How often will the monitor take a reading?
 - A. Every 20 minutes 6 AM to midnight (6 to 0 hours)
 - B. Every 40 minutes midnight to 6 AM (0 to 6 hours)
 - C. Every 30 minutes all hours
 - D. A and B

4. Please explain why it is important for a patient to have his/her arm relaxed, straight, and motionless during an ABP reading.

5. If a patient calls and says there is an error reading, what would you advise them to check?

6. For a reading to be successful for the study, how many blood pressure measurements must be recorded?
 - A. 12 during the hours of 6 AM to Midnight, and from midnight to 6 AM
 - B. 14 during a 24 hour period
 - C. 14 from 6 AM to Midnight, and 6 from Midnight to 6 AM
 - D. 24

7. What size cuff should be placed on patients for ABPM?
 - A. Follow the SpaceLabs guidelines
 - B. The same size used for that patient for manual readings (exception: 'XL' for thigh cuff users)
 - C. Whatever fits around the arm best

8. How often do I need to replace the 4 AAA batteries in the monitor?
 - A. Batteries can be re-used once (every two patients)
 - B. Batteries must be replaced for each 24-hour reading
 - C. The batteries last indefinitely

9. After subject jenal has repeated his second baseline (C0) ABPM (the first one was inadequate), and you are storing his ABP data in the computer, what file name do you use?
 - A. jenalb2
 - B. jenala2
 - C. jenal1b
 - D. jenal1a

10. After having worn the monitor yourself, what point do you find most helpful to tell study participants?

Passed: Yes__ No__
 Master Trainer Staff ID# _____
 Name (trainee) _____
 Staff ID # _____
 Date __ __ / __ __ / __ __ __ __

APPENDIX F

CARDIOVASCULAR RESEARCH FOUNDATION ABPM CORE LABORATORY AT LENOX HILL HOSPITAL

MAILING REQUIREMENTS

- 1. Labeled Floppy Disk**
- 2. Completed AASK ABPM Downloading, Copy Scan, and Mailing Form 171.**

A paper copy of the ABPM in case there is a problem with the floppy disk.

Federal Express to:

Katharine Lymberis
Attn: the AASK Cohort Study
Echocardiography Core Laboratory
Cardiovascular Research Foundation
55 East 59th Street
6th Floor
New York, NY 10022
Telephone: 212-851-9193
Fax: 212-851-9330
e-mail: KLymberis@crf.org

Please call anytime if you have any questions

APPENDIX G

CARDIOVASCULAR RESEARCH FOUNDATION ABPM CORE LABORATORY AT LENOX HILL HOSPITAL

DEFINING THE SOFTWARE DEFAULTS FOR AASK ABPM STUDY

ABPM Software Default Setting Set-Up Instructions for AASK Study using Setup Menu

When you install your software you will need to setup some groups and change some of the defaults in the Setup Menu.

A. Groups:

C Drive:

In the "Setup Menu", chose Groups
In the Name field, replace "Default" with AASK
Click Save
Click OK

A Drive:

Place a floppy in drive A
Go to Set up Groups
On left side under Scan Groups select (ABP Drive A)
On the right side under Group Settings change the fields to read as below
Click Save
Click OK

Name	ABP (DRIVE A:)
Import Directory	A:\SLREMOTE\IMPORT
Export Directory	A:\SLREMOTE\EXPORT
Work Directory	A:\SLREMOTE\WORK

B. Monitor Initialization Settings (See Table 1 in Section 13.3)

In Initialization Name Field Type AASK
DO NOT click on "Show results of reading", "Clinical Verification Setup" or "Display Cuff Pressures". We do not want patients to see these values.
Leave "Show clock time in" 24 hours.
Highlight Period 1
Set period 1 to Start Hour to 0 (see Table 1 in Section 13.3)
Start period 1 End Hour to 6

Set period 1 Cycle Time to 30
 Remove check in “Tone” box with a click
 First Line in Box should read as follows:

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

Click Change
 Highlight Period 2
 Set Period 2 Starting Hour to 6
 Set Period 2 Ending Hour to 0
 Set Period 2 Cycle time to 30
 Set Period 2 Tone to Y by clicking the “Tone Box”

Second Line in Box should read:

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

Click Change
 Choose Save
 Set Default to AASK
 Click OK
 If screen appears with “Update with modified data”, click Yes

C. Diary – leave as is

D. Physicians – Select New and change to put in your site information

E. Communications – In Direct Port Chose Com 1 or Com 2, depending on your local configuration.

F. Statistical Settings:

In Statistical Name Field type AASK
 Set the following autolimits for data arrays:
 Systolic Max at 250
 Systolic Min at 70
 Diastolic Max at 180
 Diastolic Min at 40
 MAP Max at 204
 MAP Min at 40
 PP Max at 210
 PP Min at 20
 Keep heart rate setting as is.
 Select “Save”

Highlight Period 1
 Set period 1 to Start Hour to 0 (see table 1)
 Start period 1 Ending Hour to 6
 Set Systolic to 120
 Set Diastolic to 80

Click Change
Highlight Period 2
Set Period 2 Starting Hour to 6
Set Period 2 Ending Hour to 0
Set Systolic to 140
Set Diastolic to 90
Click Change
Choose Save
Set Default to AASK
Click OK

G. Report Sequence – Keep as is

APPENDIX H
CARDIOVASCULAR RESEARCH FOUNDATION
CORE LABORATORIES
TELEPHONE DIRECTORY

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Director, Cardiovascular Research Foundation

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Cardiovascular Research Foundation
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CHAPTER 14. MEASURING ABPM INFORMATION AT THE CVD CORE LABORATORY AND TRANSMITTING DATA TO THE DCC

14.1 Clinical Center Labeling of the ABPM Disk

The ABPM disks are sent to Katharine Lymberis at CRF. The following information should be on all disks:

1. The study name
2. The center number
3. PID number
4. Name Code
5. ABPM date
6. Name of coordinator
7. Type of procedure
8. Cycle – e.g. A1, or A2
9. Comments

14.2 CRF Labeling, Copying and Data Transmission

Katharine Lymberis, at the core laboratory, labels the disk with the date received. Labels are then printed and placed on the individual disks. After the disks are labeled the following steps are taken:

1. The disk is then placed in a Federal Express envelope by site and date received. It is preferable that each patient has a separate disk as each patient has an individual chart.
2. CRF personnel then checks each patient folder for the disk, copy of the scan, and the Form 171.
3. The disk is checked for ID#, cycle, and number of readings, and 24 hour clock in the statistical summaries.
4. The disk is then copied to the appropriate network folder designated for storing data from that site number.
5. After the file is transferred to the “work” folder, the scan group is set to **EXPORT**. The completed records are then selected to export. When initiating a data export, these files are moved to the “Work” folder.
6. Select records to export and hit enter. For each record select **PCI** export format, and name the file according to the display on the screen. Filename – e.g. **LEEVI a1**, then proceed through all files selected and repeat steps. The resulting file type is an **RPT** file. These files can be found in the “Export” folder. These are then converted to a text file (open the RPT file in notepad, and then save as existing file name and add .txt to the end of the name of each file).
7. The converted text files are moved from the “export” folder to the “import” folder. At that point there is an automated import routine inside the ABPM Access database that reads through the import folder and creates a table for each text file. The table’s title is “Imported _file_six digit PID”.

8. An automated program reads through all newly imported tables and converts the content of those files into format **.CSV** requested by the Cleveland Clinic.
9. Another automated program is run to clear the files removing any empty spaces that are not necessary. The resulting file is a table consisting of records of all recently imported patient files.
10. That file is exported manually from Access into a comma delimited text file. The name of the text file is **ABPM**, followed by six numeric characters representing the date the file was created, e.g. 032003.
11. The text file is then uploaded to the Cleveland Clinic server via a Secure Shell protocol.

CHAPTER 15. CLINICAL CENTER DATA COLLECTION AND PROCESSING ECGS FOR THE CVD CORE LABORATORY

15.1 Guidelines For Obtaining Resting ECGs

To ensure high quality ECG acquisition, investigators should follow the same procedure for all patients.

In general all ECGs must be acquired in the following manner:

1. 12 Lead ECG.
2. 25 mm per second paper speed.
3. Confirmation of calibration of 10mm to 1mV.
4. The electrode site should be shaved and rubbed with alcohol to facilitate electrode adhesion.
5. Lead placement should be carried out in the following fashion:

Lead V1: Fourth ICS space at the right of the sternal border.

Lead V2: First locate the sternal angle, V2 will be located at the fourth ICS space to the left of the sternal border.

Lead V3: Position equidistant between lead V2 and V4.

Lead V4: Fifth ICS space in the midclavicular line.

Lead V5: Fifth ICS space at the level of the anterior axillary line.

Lead V6: Fifth ICS space at the level of the midaxillary line.

Lead RL: Right lower leg above the inner ankle or as close as the electrode will reach.

Lead LL: Left lower leg above the inner ankle or as close as the electrode will reach.

Lead RA: Right inner right arm above the wrist.

Lead LA: Left inner right arm above the wrist.

6. To ensure proper lead placement, electrode cable should be connected by following this order:
 - Right leg
 - Left leg
 - Right arm
 - Left arm
 - V1
 - V2
 - V3
 - V4
 - V5
 - V6

7. While recording the ECG, the relaxed patient should be in supine position and breathing normally. It is important to instruct the patient in advance so that they understand the importance of refraining from talking and moving.
8. The following problem should be checked for before the resting ECG is considered of adequate quality. The following abnormalities should be ruled out:
 - a. Lead reversal: Suspect lead reversal when Lead I is negative, Lead AVR is positive or when the precordial leads fail to show R wave progression from V1 to V6.
 - b. Missing Leads: This is identified by a flat line in one or more leads.
 - c. Excessive Baseline Drifts: This could be avoided by proper skin preparation.
 - d. Artifacts: These may be caused by defective electrodes or lead wires, or poor patient preparation.
9. **Alerts:** The clinic physician should be notified when any of the following are observed:
 - a. Acute myocardial injury.
 - b. Bradycardia Heart Rate < 45 BPM..
 - c. Ventricular Tachycardia Heart Rate > 130 BPM
 - d. Atrial Fibrillation.
 - e. Atrial Flutter.

15.2 Labelling

A 12 lead ECG must be obtained on all patients at baseline and annually. A Central ECG is obtained at C0, C24 and C48 and is sent to the ECG Core Laboratory. At C12, C36 and C60 a local ECG is performed at the clinical center.

Each ECG must be clearly labeled with:

Patient I.D. number

Patient name code

Clinical site number

ECG date (mm/dd/yyyy)

Time related to procedure (pre-procedure, post-procedure, pre-discharge, follow-up)

Military time (24 hours)

CHAPTER 16. READING ECGS AT THE CVD CORE LAB AND TRANSMITTING DATA TO THE DCC

16.1 Reading and Interpretation of ECGs

The original ECG will be mailed to ECG Core Lab at the CRF to the attention of Katharine Lymberis. Upon receipt of the ECG, it will be checked for the conformation of all pertinent information as listed above along with the quality of the ECG. Mr. Ejaz Siddiqui will perform quality assurance. ECGs not meeting quality standards will be excluded from the study.

Once a week, at the CRF Core Lab, each ECG will be read by Drs. Michael Farkouh and David Baran (Cardiology Faculty at the Mount Sinai School of Medicine). Each read ECG would then be over read and signed by Ejaz Siddiqui. Final interpretation will be based upon the agreement of at least two of the three readers.

The certified ECGs will then be returned to Katharine Lymberis, who will mail them back to the study sites. A copy of the certified ECGs will be kept in a secure location at the CRF.

16.2 Shipping Requirements

A 12 lead ECG must be obtained and sent to the Core Laboratory at baseline, C24 and C48.

Please make sure that every ECG sent to the Core lab is labeled with the following information:

Each ECG must be clearly labeled with a pre-printed label, which includes:

Clinical Site Number

Patient ID Number

Patient Name Code

ECG Date (dd/mm/yyyy)

Time related to study entry (Baseline, 2nd year, 4th year, other)

Use Military time (24hrs)

Send original ECG to:

Attn: Katharine Lymberis

THE AASK TRIAL

ECG Core Laboratory

Cardiovascular Research Foundation

55 East 59th Street, 6th Floor

New York, New York 10022

TEL: 212-851-9193

FAX: 212-851-9330

16.3 ECG Core Laboratory Directory

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For questions regarding protocol requirements, receipt of data, and confirmation reports contact Katharine Lymberis at (212) 851-9193.

16.4 Abbreviations

APC Atrial premature contraction	SA Sinoatrial
AV Atrioventricular	SVT Supraventricular tachycardia
COPD Chronic obstructive pulmonary	VA Ventriculoatrial
LAFB Left anterior fascicular block	VF Ventricular fibrillation
LBBB Left bundle branch block	VPC Ventricular premature contraction
LPFB Left posterior fascicular block	VT Ventricular tachycardia
LVH Left ventricular hypertrophy	WPW Wolff-Parkinson-White
MI Myocardial infarction	RVH Right ventricular hypertrophy
RBBB Right bundle branch block	

16.5 Borderline Normal ECG or Normal Variant

Early repolarization

Juvenile T waves

S wave in leads I, II, and III (S₁ S₂ S₃ pattern)

Note: Present in up to 20% of healthy adults.

RSR' or rSr' in lead V₁ with:

QRS duration <0.10 seconds and <7 mm in height, *and*

r' amplitude smaller than r or S waves

Note: Seen in 2% of normals.

Note: Can also be seen in pathological states:

RVH

Posterior MI

Skeletal deformities (pectus excavatum, straight back syndrome)

High electrode placement of V₁ (in 3rd intercostal space instead of 4th)

Incorrect Electrode Placement

Most commonly:

Limb lead reversal (reversal of right and left arm leads)

Resultant ECG mimics dextrocardia with inversion of the P-QRS-T in leads I and aVL

Note: To distinguish between these conditions, look at precordial leads:

dextrocardia shows reverse R wave progression, while limb lead reversal shows normal R wave progression.

Precordial lead reversal:

Typically manifests as an unexplained decrease in R wave voltage, in two consecutive leads (e.g., V₁.V₂) with a return to normal R wave progression on the following leads

Artifact

Commonly due to tremor

Parkinson's tremor simulates atrial flutter with a rate of 300 per minute (4-6 per second)

Physiologic tremor rate is 500 per minute (7-9 per second)

Most prominent in limb leads

Other common artifacts

AC electrical interference

Skeletal muscle fasciculations

16.6 Atrial Rhythms

Sinus Rhythm

Normal P wave axis and morphology

Atrial rate is 60-100 per minute and regular (PP interval varies by <0.16 seconds or 10%)

Sinus Arrhythmia

Normal P wave morphology and axis

Gradual phasic change in PP interval (may sometimes be abrupt)

Longest and shortest PP intervals vary by >0.16 seconds or 10%

Note: Sinus arrhythmia differs from "ventriculophasic" sinus arrhythmia, the latter of which occurs in the setting of partial or complete heart block.

Sinus Bradycardia (<60)

Normal P wave axis and morphology)

Rate <60 per minute

Note: If the atrial rate is <40 per minute, think of 2:1 sinoatrial exit block

Sinus Tachycardia (>100)

Normal P wave axis and morphology

Rate >100 per minute

Note: P wave amplitude often increases and PR interval often shortens with increasing heart rate (eg, during exercise)

Sinus Pause or Arrest

PP interval (pause) greater than 1.6-2.0 seconds

Sinus rhythm resumes at a PP interval that is not a multiple of the basic sinus PP interval

Note: If sinus rhythm resumes at a multiple of the basic PP, consider sinoatrial exit block

Note: Sinus pause/arrest is due to transient failure of impulse formation at the SA node

Note: Sinus pauses must be differentiated from:

Sinus arrhythmia: Phasic, gradual change in PP interval

Second-degree sinoatrial exit block, Mobitz I (Wenckebach):

Progressive shortening of PP interval until a P wave fails to appear.

Second-degree sinoatrial exit block, Mobitz II: Resumption of sinus rhythm at a PP interval that is a multiple (e.g., 2x, 3x, etc.) of the basic sinus rhythm

Third-degree sinoatrial exit block (Complete failure of sinoatrial conduction; cannot be differentiated from complete sinus arrest on surface ECG. Abrupt change in autonomic tone “Pseudo” sinus pause due to non-conducted APCs: P wave appears to be absent but is actually buried in the T wave — look for subtle deformity of the T wave just preceding the pause to detect non-conducted atrial premature complexes

Sinoatrial (SA) Exit Block

First-degree: Conduction of sinus impulses to the atrium is delayed, but 1:1 response is maintained; not detectable on surface ECG

Second-degree: Some sinus impulses fail to capture the atria (i.e., intermittent absence of a P wave)

Type I (Mobitz I):

P wave morphology and axis consistent with a sinus node origin

“Group beating” with:

- (1) Shortening of the PP interval leading up to pause
- (2) Constant PR interval
- (3) PP pause less than twice the normal PP interval

Type II (Mobitz II):

Constant PP interval followed by a pause that is a multiple (e.g., 2x, 3x, etc.) of the normal PP Interval

Note: The pause may be slightly less than twice the normal PP interval but is usually within 0.10 seconds

Third-degree: Complete failure of sinoatrial conduction; cannot be differentiated from complete sinus arrest

Ectopic Atrial Rhythm

P wave axis or morphology different from sinus node

Rate <100 per minute

PR interval >0.11 seconds

Note: Inverted P waves in II, III, aVF suggest either an AV junctional rhythm with retrograde atrial activation or a low atrial rhythm. To distinguish between these mechanisms, measure the PR interval:

PR > 0.11 seconds suggests a low atrial rhythm

PR ≤ 0.11 seconds suggests an AV junctional rhythm

Wandering Atrial Pacemaker

P waves with 3 morphologies

Rate <100 per minutes

Varying PR, RR, and RP intervals

Note: May be confused with:

Sinus rhythm with multifocal APCs: Sinus rhythm with multifocal APCs demonstrates one dominant atrial pacemaker (i.e., the sinus node); in wandering atrial pacemaker, *no* dominant atrial pacemaker (i.e., no dominant P wave morphology) is present.

Atrial fibrillation/flutter with a moderate ventricular response: In atrial fib/flutter, there is lack of an isoelectric baseline; in wandering atrial pacemaker, a distinct isoelectric baseline is present.

Note: P waves may be blocked (i.e., not followed by a QRS complex), or may be conducted with a narrow or aberrant QRS complex.

Atrial Premature Complexes, Normally Conducted P Wave that is Abnormal in Configuration and Premature Relative to the Normal PP Interval

QRS complex is similar in morphology to the QRS complex present during sinus rhythm

Note: The PR interval may be normal, increased, or decreased.

Note: The post-extrasystolic pause is usually non-compensatory (i.e., premature P to subsequent P wave interval is less than two PP intervals). However, an interpolated APC or a full compensatory may be evident when sinoatrial (SA) entrance block is 1) present and the SA node is not reset.

Atrial Premature Complexes, Non-Conducted

Premature P wave with abnormal morphology not followed by a QRS-T complex

Note: The sinus node is usually reset, resulting in a non-compensatory pause

Note: P waves are often hidden in the preceding T wave — when you see an RR pause, look for a deformed T wave immediately preceding the pause to identify the presence of a non-conducted atrial premature beat.

Atrial premature complexes with **aberrant intraventricular conduction**

P wave occurs very early relative to the normal PP interval

QRS morphology is most often RBBB pattern, but can be LBBB or variable Atrial tachycardia (regular, sustained, 1:1 conduction)

P wave axis or morphology different from sinus node

Three or more beats in succession at an atrial rate of 100-180 per minute (may be up to 240 per minute)

Regular rhythm (constant RR interval), except for a warm-up period in the automatic type

QRS complex follows each P wave

QRS morphology usually resembles QRS during sinus rhythm, but may be wide and bizarre if aberrant

PR interval may be within normal limits or prolonged

Nonspecific ST-T changes may occur

Atrial Tachycardia, Repetitive (Short Paroxysm)

Recurring short runs of atrial tachycardia, interrupted by normal sinus rhythm

Atrial Tachycardia, Multifocal (Chaotic Atrial Tachycardia)

Atrial rate >100 per minute

P waves with ≥ 3 morphologies

Varying PR, RR and RP intervals

Note: Multifocal atrial tachycardia may be confused with:

Sinus tachycardia with multifocal APCs, which demonstrates one dominant atrial pacemaker (i.e., the sinus node). In contrast, in multifocal atrial tachycardia, no dominant atrial pacemaker (i.e., no dominant P wave morphology) is present.

Atrial fibrillation/flutter, in which there is lack of an isoelectric baseline. In contrast, multifocal atrial tachycardia demonstrates a distinct isoelectric baseline and P waves.

Note: P waves may be blocked (i.e., not followed by a QRS complex), or may be conducted with a narrow or aberrant QRS complex

Atrial tachycardia with AV block

P wave axis or morphology different from sinus node

Atrial rate of 150-240 per minute (may be as low as 100 per minute)

Isoelectric intervals between P waves in all leads

Second- or third-degree AV block

Atrial rhythm is regular (but may see ventriculophasic arrhythmia)

Note: May be secondary to digoxin toxicity

Note: May be confused with atrial flutter. Atrial tachycardia with AV block has a distinct isoelectric baseline between P waves, whereas atrial flutter does not (except in lead V₁).

Supraventricular Tachycardia, Unspecified

Regular rhythm

Rate >100 per minute

P waves not easily identified

QRS complex is usually narrow (but occasionally aberrant)

Note: If rate is 150 per minute, atrial flutter with 2:1 block may be present.

Supraventricular Tachycardia (Paroxysmal)

Onset and termination of SVT is sudden.

SVT is episodic and does not persist throughout the entire tracing.

May see retrograde atrial activation.

Atrial Flutter

Rapid regular atrial undulations (flutter or "F" waves) at 240-340 per minute

Note: Flutter rate may be faster in children, and slower in the presence of antiarrhythmic drugs (Type IA, IC, III) and massively dilated atria.

Typical atrial flutter morphology usually present:

Leads II, III, AVF: Inverted F waves without an isoelectric baseline (“picket fence” or “sawtooth” appearance)

Lead V₁: Small positive deflections with a distinct isoelectric baseline

QRS complex may be normal or aberrant

Rate and regularity of QRS complexes depend on the AV conduction sequence

AV conduction ratio (ratio of flutter waves to QRS complexes) is usually fixed (e.g., 2:1, 4:1), but may vary.

Note: Conduction ratios of 1:1 and 3:1 are uncommon. In untreated patients, $\geq 4:1$ block suggests the co-existence of AV conduction disease. Complete heart block with a junctional or ventricular escape rhythm may be present.

Note: Think digitalis toxicity when complete heart block with junctional tachycardia is present.

Note: Flutter waves can deform QRS, ST and/or T to mimic intraventricular conduction delay and or myocardial ischemia.

Atrial Fibrillation

P waves absent

Atrial activity is totally irregular and represented by fibrillatory (f) wave of varying amplitude, duration and morphology, causing random oscillation of the baseline.

Note: Atrial activity is best seen in the V₁, V₂ and the inferior leads (II, III, aVF).

Ventricular rhythm is irregularly irregular

Note: If the RR interval is regular, third-degree AV block is present.

Note: Digoxin toxicity may result in regularization of the QRS due to complete heart block with junctional tachycardia.

Ventricular rate is usually 100-180 per minute in the absence of drugs

Note: If the rate without AV blocking drugs is less than 100 beats per minute, AV conduction system disease is likely to be present.

Note: Think Wolff-Parkinson-White if the ventricular rate is >200 per minute and the QRS is >0.12 seconds.

Note: Conditions mimicking atrial fibrillation include:

Multifocal atrial tachycardia

Paroxysmal atrial tachycardia with block

Atrial flutter

Retrograde Atrial Activation

Inverted P waves in leads II, III and aVF

Note: Look for retrograde P waves after ventricular premature complexes and other junctional, ventricular, or low ectopic atrial rhythms.

16.7 AV Junctional Rhythms

AV Junctional Premature Complexes

Premature QRS complex (relative to the basic RR interval), which may be narrow or aberrant Inverted P waves in leads II, III, aVF and upright P waves in leads I and aVL is commonly seen.

Note: The atrium may occasionally be activated by the sinus node, resulting in a normal sinus P wave. This occurs when retrograde block exists between the AV junctional focus and the atrium.

Note: The P wave may precede the QRS by ≤ 0.11 seconds (retrograde atrial activation), may be buried in the QRS (and not visualized), or may follow the QRS complex.

Note: A constant coupling interval and non-compensatory pause are usually present.

AV Junctional Escape Complexes

Rate is typically 40-60 per minute

Atrial mechanism may be sinus rhythm, paroxysmal atrial tachycardia, atrial flutter, or atrial fibrillation

QRS morphology is similar to the sinus or supraventricular impulse

Note: QRS complex occurs as a secondary phenomenon in response to decreased sinus impulse formation or conduction, high-degree AV block, or after the pause following termination of atrial tachycardia, atrial flutter, or atrial fibrillation.

AV Junctional Rhythm, Accelerated

Regular QRS rhythm at rate >60 per minute

P wave may proceed, be buried in, or follow the QRS complex

QRS is usually narrow but may be wide if aberrant or pre-existing IVCD

Relationship between atrial and ventricular rates may vary:

If retrograde block is present, the atria remain in sinus rhythm and AV dissociation will be present

If retrograde atrial activation occurs, a constant QRS-P interval is usually present (occasionally there is 2:1 VA conduction)

Note: Think digitalis toxicity if atrial fibrillation or flutter with a regular RR is seen - this often represents complete heart block with accelerated junctional rhythm.

AV Junctional Rhythm (Rate < 60 /minute)

P wave and QRS complex

RR interval of escape rhythm is usually constant (< 0.04 seconds variation)

May have isorhythmic AV dissociation

16.8 Ventricular Rhythms

Ventricular Premature Complex(es), Uniform, Fixed Coupling

Requires all of the following:

A wide, notched or slurred QRS complex that is:

Premature relative to the normal RR interval, *and*

Not preceded by a P wave

Note: QRS is almost always >0.12 seconds.

Note: Initial direction of the QRS is often different from the QRS during sinus rhythm.

Secondary ST & T wave changes in a direction opposite to the major deflection of the QRS (i.e., ST depression & T wave inversion in leads with a dominant R wave; ST elevation and upright I wave in leads with a dominant S wave or QS complex)

Coupling interval (relation of VPCs to the preceding QRS) is constant (or varies by <0.08 seconds)

Morphology of VPCs in any given lead is the same (i.e., uniform)

Note: Retrograde capture of atria may occur

Note: A full compensatory pause (PP interval containing the VPC is twice the normal PP interval) is usually evident, and requires undisturbed sinus depolarization due to:

Ventriculoatrial (VA) conduction block

Sinoatrial (SA) entrance block if atrial capture occurs

SA node discharge prior to arrival of retrograde wavefront

Ventricular Premature Complexes, Nonfixed Coupling

Relationship of VPCs to preceding QRS (coupling interval) is variable

Ventricular Premature Complex(es), Multiform

VPCs with ≥ 2 morphologies

Note: Although multiform VPCs are usually multifocal in origin (i.e., originate from more than one ventricular focus), a single ventricular focus can produce VPCs of varying morphology.

Ventricular Premature Complexes, in Pairs (Two Consecutive)

Two consecutive ventricular premature complexes of not necessarily the same morphology

Ventricular Parasystole

Ventricular ectopic beats (VEB) occur at a rate of 30-50 per minute (but may range from 20- 400 per minute, depending upon the degree of exit block and the refractoriness of the ventricle)

Resultant ventricular premature complexes (VPC) vary in relationship to the preceding sinus or supraventricular beats (i.e., nonfixed coupling)

VPCs typically manifest the same morphology (which resembles a VPC) unless fusion occurs

Note: Fusion complexes are commonly seen but are not required for the diagnosis.

Note: When the ectopic ventricular focus originates on the same side as a bundle branch block, the resulting fusion complex can be narrow. All interectopic intervals are a multiple (2x, 3x, etc.) of the shortest interectopic interval present

Note: Ventricular parasystole is due to the presence of an ectopic ventricular focus that activates the ventricles independent of the basic sinus or supraventricular rhythm, and is protected from depolarization by an entrance block.

Note: Think of parasystole when you see ventricular premature complexes with nonfixed coupling and fusion beats.

Ventricular Tachycardia (≥ 3 Consecutive Beats)

Rapid succession of three or more premature ventricular beats at a rate > 100 per minute

RR interval is usually regular but may be irregular

Abrupt onset and termination of arrhythmia is evident

AV dissociation is common

On occasion, retrograde atrial activation and capture occur

Note: Look for ventricular capture complexes and fusion beats as markers for VT.

Note: In the setting of a wide QRS tachycardia, certain findings may help distinguish ventricular tachycardia from supraventricular tachycardia with aberrancy (Table 1).

Accelerated Idioventricular Rhythm

Regular or slightly irregular ventricular rhythm

Rate of 60-110 per minute

QRS morphology similar to VPCs

AV dissociation is often present

Ventricular capture complexes and fusion beats are common

Table 1

Origin of Wide QRS Tachycardia

	FAVORS VT	FAVORS SVT
QRS morphology	Similar to VPCs	Similar to sinus rhythm
or		
Tachycardia initiated by		
AV dissociation	Yes	No
Capture or fusion beats	Yes	No
QRS duration when QRS is narrow during sinus rhythm	> 0.14 sec. if RBBB morphology; > 0.16 sec. if LBBB	
QRS deflection in precordial leads	All positive or negative (concordance)	Some positive and some negative (discordance)
Axis	Left or northwest	
RSR' in V_1	R wave taller than R'	R' taller than R wave

Ventricular Escape Beats or Rhythm

Regular or slightly irregular ventricular rhythm

Rate of 30-40 per minute (can be 20-50 per mm)

QRS morphology similar to VPCs

Note: QRS complex occurs as a secondary phenomenon in response to decreased sinus impulse formation or conduction, high-degree AV block, or after the pause following termination of atrial tachycardia, atrial flutter, or atrial fibrillation.

Ventricular Fibrillation

An extremely rapid and irregular ventricular rhythm demonstrating:

Chaotic and irregular deflections of varying amplitude and contour, *and*

Absence of distinct P waves, QRS complexes, or T waves

16.9 Atrioventricular Interactions

Fusion Complexes

Simultaneous activation of the ventricle from two sources, resulting in a QRS complex intermediate in morphology between the QRS complexes of each source

Note: Fusion complexes may be seen with:

Ventricular premature complexes

Ventricular tachycardia

Ventricular parasystole

Accelerated idioventricular rhythm

Wolff-Parkinson-White Syndrome

Paced rhythm

Reciprocal (echo) complexes

An impulse activates a chamber (atria or ventricle), returns to site of origin, and reactivates the same chamber again

A form of nonsustained reentry

Ventricular Capture Complexes

Occurs when an atrial impulse is conducted to and stimulates the ventricles during ventricular tachycardia. The “captured” ventricle results in a:

Fusion complex *or*

QRS complex similar to that during sinus rhythm

Note: The presence of a ventricular capture complex in the setting of a wide QRS tachycardia

strongly suggests the diagnosis of ventricular tachycardia.

AV dissociation

Atrial and ventricular rhythms are independent of each other, and the Ventricular rate is equal to or faster than the atrial rate

Note: AV dissociation is always a secondary phenomenon resulting from some other disturbance of cardiac rhythm. Examples include:

Slowing of the atrial rate (Sinus bradycardia, sinus arrest, sinoatrial exit block), below the intrinsic rate of a subsidiary AV junctional or ventricular pacemaker, or

Acceleration of a subsidiary pacemaker (e.g., junctional or ventricular tachycardia) to a rate faster than the normal sinus rate.

Ventriculophasic Sinus Arrhythmia

PP interval containing a QRS complex is less than the PP interval without a QRS complex

Note: Occurs in 30-50% of patients with partial or complex AV block.

16.10 AV Conduction Abnormalities

AV Block, 1st Degree

PR interval >0.20 seconds (usually 0.2-0.40 seconds but may be as long as 0.80 seconds)

Each P wave is followed by a QRS complex

AV Block, 2 - Mobitz Type I (Wenckebach)

Progressive prolongation of the PR interval and shortening of the RR interval until a P wave is blocked, *and the*

RR interval containing the nonconducted P wave is less than two PP intervals

Note: Classical Wenckebach periodicity may not always be evident, especially when sinus arrhythmia is present or an abrupt change in autonomic tone occurs.

Note: Mobitz Type I results in “group” or “pattern beating” due to the presence of non-conducted P waves. Other causes of group beating include:

Blocked APCs

Type II second-degree AV block

Concealed His-bundle depolarizations

AV Block, 2 - Mobitz Type II

Regular sinus or atrial rhythm with intermittent non-conducted P waves and no evidence for atrial prematurity, *and*

PR interval in the conducted beats is constant, *and*

RR interval containing the non-conducted P wave is equal to two PP intervals.

Note: 2:1 AV block can be Mobitz Type I or II. Features suggesting (but not proving) one mechanism over another are listed in Table 2.

Table 2. Features Suggesting the Mechanism of 2:1 AV Block

Mobitz Type I

QRS duration

Response to maneuvers that increase heart rate & AV conduction (e.g., atropine, exercise)

Response to maneuvers that reduce heart rate & AV conduction (e.g., carotid sinus massage)

Develops during acute MI Other

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Block improves
Block worsens
Inferior MI
Mobitz I on another part of ECG
Mobitz Type Ii
Wide
Block worsens
Block improves
Anterior Nil
History of syncope

AV block, 2:1

Regular sinus or atrial rhythm with two P waves for each QRS complex (i.e., every other P wave is non-conducted)

Note: Can be Mobitz Type I or II second-degree AV block (see Table 2).

AV Block, 3rd Degree

Atrial and ventricular rhythms are independent of each other

Atrial rate is usually faster than ventricular rate

Ventricular rhythm is maintained by a junctional or idioventricular escape rhythm or a ventricular pacemaker.

Note: Ventriculophasic sinus arrhythmia may be present in 30-50%.

Note: Complete heart block may present with an atrial rate slower than the ventricular escape rate. This is identified by the presence of nonconducted P waves when the AV node and ventricle are not refractory.

AV Block, Variable

Varying degrees of AV block (10, 20,)

Note: Consider this diagnosis in atrial flutter with variable intervals between flutter waves and R waves after ruling out third-degree AV block

Short PR interval (with sinus rhythm and normal QRS duration)

Normal P wave axis and morphology

PR interval <0.12 seconds

No delta wave (QRS <0.11 seconds)

No sinus rhythm with AV dissociation

Wolff-Parkinson-White Pattern

Normal P wave axis and morphology

PR interval <0.12 seconds (rarely >0.12 seconds)

Initial slurring of QRS (delta wave) resulting in an abnormally wide QRS (>0.10 seconds)

Secondary ST-T wave changes (opposite in direction to main deflection of QRS)

Note: PJ interval (beginning of P wave to end of QRS complex) is constant and \leq 0.26 seconds

Note: Think WPW when atrial fibrillation or flutter is associated with a QRS that varies in width (generally wide) and has a rate >200 per minute

16.11 Intraventricular Conduction Disturbances

RBBB, Incomplete

RBBB morphology (rSR' in V₁) with a QRS duration between 0.09 and less than 0.12 seconds

Note: Other causes of RSR' pattern <0.12 seconds in lead V₁ include:

Normal variant (present in 2% of healthy adults)

Right ventricular hypertrophy

Posterior wall MI

Incorrect lead placement (electrode for lead V₁ placed in 3rd instead of 4th intercostal space)

Skeletal deformities (e.g., pectus excavatum)

RBBB, Complete

Prolonged QRS duration (≥ 0.12 seconds)

Secondary R wave (R') in leads V₁ and V₂ (rsR' or rSR') with R' usually taller than the initial R wave

Delayed onset of intrinsicoid deflection (beginning of QRS to peak of R wave >0.05 seconds) in V₁ and V₂

Secondary ST & T-wave changes (downsloping ST segment, T-wave inversion) in leads V₁ and V₂

Wide slurred S wave in leads I, V₅, and V₆

Note: In RBBB, mean QRS axis is determined by the initial unblocked 0.06-0.08 seconds of QRS, and should be normal unless left anterior fascicular block or left posterior fascicular block is present.

Note: RBBB does not interfere with the ECG diagnosis of ventricular hypertrophy or Q-wave MI.

Left Anterior Fascicular Block

Left axis deviation with mean QRS axis between -45 and 90 degrees.

qR complex (or an R wave) in leads I and aVL

rS complex in lead III

Normal or slightly prolonged QRS duration (0.08-0.10 seconds)

No other factors responsible for left axis deviation:

LVH

Inferior wall MI

Emphysema (chronic lung disease)

Left bundle branch block

Ostium primum atrial septal defect

Severe hyperkalemia

Note: LAFB may result in a false-positive diagnosis of LVH based on voltage criteria using leads I or aVL.

Note: Poor R-wave progression is common.

Note: Left anterior fascicular block can mask the presence of inferior wall MI.

Left Posterior Fascicular Block

Right axis deviation with mean QRS axis between ± 100 and $+180$

S₁ Q₃ pattern (deep S wave in lead I; Q wave in lead III sometimes seen)

Normal or slightly prolonged QRS duration (0.08-0.10 seconds)

No other factors responsible for right axis deviation:

RVH

Vertical heart

Emphysema (chronic lung disease)

Pulmonary embolism

Lateral wall MI

Dextrocardia

Lead reversal

Wolff-Parkinson-White

Note: Left posterior fascicular block can mask the presence of lateral wall MI.

LBBB, with ST-T Waves Suggestive of Acute Myocardial Injury or Infarction

Fulfills criteria for LBBB (also valid for LBBB due to artificial pacemaker)

Three criteria with independent value for diagnosing acute myocardial injury in setting of LBBB (in descending order of significance):

ST elevation > 1 mm concordant to (same direction as) the major deflection of the QRS

ST depression > 1 mm in V₁, V₂, or V₃

ST elevation > 5 mm discordant with (opposite direction to) the major deflection of the QRS

LBBB, Complete

Prolonged QRS duration (≥ 0.12 seconds)

Delayed onset of intrinsicoid deflection in leads I, V₅, V₆ (i.e., beginning of QRS to peak of R wave > 0.05 seconds)

Broad monophasic R waves in leads I, V₅, V₆ that are usually notched or slurred

Secondary ST & T wave changes opposite in direction to the major QRS deflection

i.e., ST depression & T wave inversion in leads I, V₅, V₆; ST elevation & upright T wave in leads V₁ and V₂)

rS or QS complex in right precordial leads

Note: Left axis deviation may be present

Note: LBBB interferes with determination of QRS axis and the ECG diagnoses of ventricular hypertrophy and acute MI.

LBBB, Intermittent

Note: More commonly seen at high rates (tachycardia-dependent) but may be bradycardia-dependent as well.

Intraventricular Conduction Disturbance, Nonspecific Type

QRS ≥ 0.11 seconds in duration but morphology does not meet criteria for LBBB (item 70 or RBBB), or abnormal QRS notching without prolongation

Note: IVCD may be seen with:

Antiarrhythmic drug toxicity (especially Type IA and IC agents)
Hyperkalemia

LVH

Wolff-Parkinson-White Hypothermia
Severe metabolic disturbances

Aberrant Intraventricular Conduction with Supraventricular Arrhythmia

Note: See criteria to distinguish between SVT with aberrancy vs. VT.

P WAVE ABNORMALITIES

Right Atrial Abnormality

Upright P wave: >2.5 mm in leads II, III, and aVF (P-pulmonale), or $\sim >1.5$ mm in leads V_1 or V_2 .

P wave axis shifted rightward (i.e., axis ≥ 70 degree)

Note: In up to 30% of cases, P pulmonale may actually represent left atrial enlargement. Suspect this possibility when left atrial abnormality is present in lead V_1 .

Left Atrial Abnormality

Notched P wave with a duration >0.12 seconds in leads II, III or aVF (P-mitrale), or Terminal negative portion of the P wave in lead ≥ 1 mm deep and ≥ 0.04 seconds in duration (i.e., one small box deep and one small box wide)

Bi-atrial enlargement is suggested by any of the following:

Large biphasic P wave in $V_1 \geq 0.04$ seconds with:

An initial positive amplitude > 1.5 mm, *and*

A. terminal negative amplitude ≥ 1 mm

Tall peaked P waves (>1.5 mm) in the right precordial leads (V_1 - V_3) and wide notched P waves in the left precordial leads (V_5 - V_6)

P wave amplitude >2.5 mm in the limb leads with a duration >0.12 seconds

Nonspecific Atrial Abnormality

Abnormal P wave morphology not fulfilling criteria for right or left atrial abnormality

16.12 Abnormalities of QRS Voltage or Axis

Low Voltage, Limb Leads Only

Amplitude of the entire QRS complex (R+S) <5 mm in all limb leads

Low Voltage, Limb and Precordial Leads

Amplitude of the entire QRS complex (R+S) < 10 mm in each precordial lead, *and*

Amplitude of R+S < 5 mm in all limb leads

Note: Causes include:

Chronic lung disease

Pericardial effusion

Myxedema Obesity

Pleural effusion

Note: In up to 30% of cases, P pulmonale may actually represent left atrial enlargement. Suspect this possibility when left atrial abnormality is present in lead V₁.

Left atrial abnormality

Notched P wave with a duration >0.12 seconds in leads II, III or aVF (P-mitrale), *or* Terminal negative portion of the P wave in lead V₁ ≥ 1 mm deep and a 0.04 seconds in duration (i.e., one small box deep and one small box wide)

Bi-atrial enlargement is suggested by any of the following:

Large biphasic P wave in V₁ ≥ 0.04 seconds with:

An initial positive amplitude > 1.5 mm, *and*

A terminal negative amplitude a 1 mm

tall peaked P waves (>1.5 mm) in the right precordial leads (V₁-V₃) and wide notched P waves in the left precordial leads (V₅-V₆)

P wave amplitude >2.5 mm in the limb leads with a duration >0.12 seconds

Nonspecific Atrial Abnormality

Abnormal P wave morphology not fulfilling criteria for right or left atrial abnormality

16.13 Abnormalities of QRS Voltage or Axis

Low Voltage, Limb Leads Only

Amplitude of the entire QRS complex (R+S) <5 mm in all limb leads

Low Voltage, Limb and Precordial Leads

Amplitude of the entire QRS complex (R+S) < 10 mm in each precordial lead, *and*

Amplitude of R+S <5 mm in all limb leads

Note: Causes include:

Chronic lung disease

Pericardial effusion

Myxedema

Obesity

Pleural effusion

Restrictive or infiltrative cardiomyopathies

Diffuse coronary disease

Left Axis Deviation ($> -30^\circ$)

Mean QRS axis between -30° and -106°

Note: Causes include:

Left anterior fascicular block (if axis $>45^\circ$)

Inferior wall MI

LBBB

LVH

Ostium primum ASD

COPD
Hyperkalemia

Right Axis Deviation (> +1000)

Mean QRS axis between 101° and 254°

Pure right axis deviation (left posterior fascicular block) should have an S wave in lead I and a Q wave in lead III ($S_1 Q_3$ pattern)

Note: Causes include:

RVH

Vertical heart

Chronic obstructive pulmonary disease)

Pulmonary embolus

Left posterior fascicular block

Lateral wall myocardial infarction

Dextrocardia

Lead reversal

Ostium secundum ASD

Electrical Alternans

Alternation in the amplitude and/or direction of P, QRS, and/or T waves

Note: Causes include:

Pericardial effusion). (If electrical alternans involves the P QRS, and T [“total alternans”], effusion with tamponade is often present. Yet, only 12% of patients with pericardial effusions have electrical alternans.)

Severe left ventricular failure

Hypertension

Coronary artery disease

Rheumatic heart disease

Supraventricular or ventricular tachycardia deep respirations

16.14 Ventricular Hypertrophy

Left Ventricular Hypertrophy by Voltage Only

Cornell Criteria (most accurate) R wave in aVL + S wave in V_3

>24 mm in males

>20 mm in females

Other commonly used voltage-based criteria

Precordial leads (one or more)

- (1) R wave in V_5 or V_6 + S wave in V_1
>35mm if age >30 years
> 40 mm if age 20-30 years
>60mm if age 16-19 years
- (2) Maximum R wave + S wave in precordial leads > 45 mm
- (3) R wave in V_5 >26 mm
- (4) R wave in V_6 >20 mm

Limb leads (one or more)

- (1) R wave in lead I + S wave in lead II > 26mm
- (2) R wave in lead I \geq 14 mm
- (3) S wave in aVR \geq 15 mm
- (4) R wave in aVL \geq 12 mm (a highly specific finding)
- (5) R wave in aVF \geq 21 mm

Non-voltage related criteria for LVH (often seen with or without prominent voltage and ST-T changes in patients with LVH)

Note: For EGG features of RVH in the setting of chronic lung disease.

Note: Conditions that may present with right axis deviation and/or a dominant R wave and possibly mimic RVH include:

Posterior or infero-posterolateral wall MI

Right bundle branch block

Wolff-Parkinson-White syndrome (type A)

Dextroposition

Left posterior fascicular block

Normal variant (especially in children)

Combined Ventricular Hypertrophy

Suggested by any of the following:

EGG meets one or more diagnostic criteria for both isolated LVH and RVH

Precordial leads show LVH but QRS axis is $>90^\circ$

LVH *plus*:

R wave > Q wave in aVR, *and*

S wave > R wave in V₅ *and*

T wave inversion in V₁

Large amplitude, equiphasic (R~S) complexes in V₃ and V₄ (Kutz-Wachtel phenomenon)

Right atrial abnormality with LVH pattern in precordial leads

16.15 Q-Wave Myocardial Infarction

General considerations:

Age of infarct can be approximated from EGG pattern:

Probably Acute or Recent

Acute MI: Abnormal Q waves, ST elevation (associated ST depression is sometimes present in non-infarct leads)

Recent MI: Abnormal Q waves, isoelectric ST segments, ischemic (usually inverted) T waves

Probably old or age indeterminate

ST segments,

Old MI: Abnormal Q waves, isoelectric

nonspecific or normal T waves

Note: Exception: MI may be present without Q waves in:

Anterior MI: May only see low anterior R wave forces with decreasing R wave progression in leads V₂-V₅

Posterior MI: Dominant R wave and ST depression in leads V₁ -V₃ Myocardial infarction vs. injury vs. ischemia:

Infarction: Abnormal Q waves; ST segment elevation or depression; T waves inverted, normal, or upright & symmetrically peaked

Injury: ST segment elevation; Q waves absent

Ischemia: ST segment depression; T waves usually inverted; Q waves absent

Note: Exception: MI may be present without Q waves in:

Anterior MI: May only see low anterior R wave forces with decreasing R wave progression in leads V₂-V₅

Posterior MI: Dominant R wave and ST depression in leads V₁-V₃

Abnormal Q waves

Duration \geq 0.03 seconds for most leads

Duration \geq 0.04 seconds in leads III, aVL, aVF, and V₁

Significant ST elevation

1-2 mm in two or more contiguous leads

Usually with upwardly convex configuration

Can persist 48 hours to 4 weeks after MI

Note: Persistent ST elevation beyond 4 weeks suggests the presence of a ventricular aneurysm

T wave inversions may persist indefinitely

Conditions causing "pseudoinfarcts" (EKG pattern mimics myocardial infarction):

Wolff-Parkinson-White

Hypertrophic cardiomyopathy

LVH

RVH

Left anterior fascicular block

Chronic lung disease

Amyloid heart (or other infiltrative diseases)

Cardiomyopathy

Chest deformity (e.g., pectus excavatum)

Pulmonary embolism

Myocarditis

Myocardial tumors

Hyperkalemia

Pneumothorax

Lead reversal

Congenitally corrected transposition

Dextrocardia

Diagnosis of Q wave MI in the presence of bundle branch block

RBBB: Does not interfere with the diagnosis of Q wave MI; Q wave criteria apply for all infarctions

LBBB: Difficult to diagnose any infarct in the presence of LBBB. However, acute injury is sometimes apparent

Anterolateral Infarction, Recent or Probably Acute

Abnormal Q waves (duration ≥ 0.03 seconds) in leads V_4 - V_6 , accompanied by ST segment elevation

Anterior Infarction, Recent or Probably Acute

rS in V_1 , followed by

QS or QR complexes (Q wave duration ≥ 0.03 seconds) and ST segment elevation in two of leads V_2 - V_4 , or

Decreasing R wave amplitude from V_2 - V_5

Anteroseptal Infarction, Recent or Probably Acute

Abnormal Q or QS deflection in V_1 - V_3 and sometimes V_4 (Q wave duration ≥ 0.04 seconds in V_1 and ≥ 0.03 seconds in V_2 - V_4), accompanied by ST segment elevation

Note: Some electrocardiographers read anteroseptal infarction when abnormal Q waves are present in V_1 - V_2 but not in V_3 or any other leads.

Note: The presence of a Q wave in V_1 distinguishes anteroseptal from anterior infarction.

Lateral or High Lateral Infarction, Recent or Probably Acute

Abnormal Q wave in lead I (duration ≥ 0.03 seconds) and aVL (duration ≥ 0.04 seconds),

accompanied by ST segment elevation.

Note: An isolated Q wave in aVL does not qualify as a lateral MI.

Inferior (Diaphragmatic) Infarct, Recent or Probably Acute

Abnormal Q waves in at least two of leads II, III, aVF (Q wave duration ≥ 0.03 seconds in lead II ≥ 0.04 seconds in leads II and aVF), accompanied by ST segment elevation

Note: Associated ST depression is usually evident in leads I, aVL, V_1 - V_3 .

Posterior infarct, recent or probably acute

Initial R wave ≥ 0.04 seconds in V_1 and V_2 with:

R wave \geq S wave, and

ST segment depression (usually ≥ 2 mm) with upright T waves

Note: Posterior MI is usually seen in the setting of acute inferior MI.

Note: RVH, WPW, and RBBB interfere with the ECG diagnosis of posterior MI.

Anterolateral Infarction, Age Indeterminate or Probably Old

No ST segment elevation

Anterior Infarction, Age Indeterminate or Probably Old

No ST segment elevation

Anteroseptal Infarction, Age Indeterminate or Probably Old

No ST segment elevation

Lateral or High Lateral Infarction, Age Indeterminate or Probably Old

No ST segment elevation

Inferior (Diaphragmatic) Infarct, Age Indeterminate or Probably Old

No ST segment elevation

Posterior Infarct, Age Indeterminate or Probably Old

No ST segment depression characteristic of acute posterior injury

Probable Ventricular Aneurysm

ST segment ≥ 1 mm persisting 4 or more weeks after acute MI in leads with abnormal Q waves

ST, T, U WAVE Abnormalities

Normal Variant, Early Repolarization

Suggested by the following:

Elevated take-off of ST segment at the junction between the QRS and ST segment (J junction)

Concave upward ST elevation ending with a symmetrical upright T wave (often of large amplitude)

Distinct notch or slur on downstroke of R wave

Most commonly involves leads V_2 - V_5 ; sometimes seen in leads II, III, and aVF

No reciprocal ST segment depression

Note: Some degree of ST elevation is present in the majority of young healthy individuals, especially in the precordial leads.

Normal Variant, Juvenile T Waves

Suggested by the following:

Persistently negative T waves (usually not symmetrical or deep) in leads V_1 - V_3 in normal adults

T waves still upright I,II, V_5 , V_6

Note: Most frequently seen in young healthy females.

Nonspecific ST and/or T Wave Abnormalities

Slight (< 1 mm) ST depression or elevation, *and/or*

T wave flat or slightly inverted

Note: T wave is usually $\geq 10\%$ the height of the R wave

Note: Can be seen in:

Pancreatitis

Organic heart disease

Pericarditis

Drugs (e.g., quinidine)

CNS disorders

Electrolyte disorders (e.g., hypokalemia)
LVH
Hyperventilation
RVH
Hypothyroidism
Bundle branch block
Stress
Healthy adults (normal variant)

ST and/or T Wave Abnormalities Suggesting Myocardial Ischemia

Ischemic T wave changes
Biphasic T waves with or without ST depression
Symmetrical or deeply inverted T waves
Note: QT interval is usually prolonged.
Note: Reciprocal T wave changes may be evident (e.g., tall upright T waves in inferior leads with deeply inverted T waves in anterior leads).
Note: Prominent U waves (upright or inverted) are often present.
Note: Tall upright T waves may also be seen in:
Normal healthy adults
CNS disorders
Hyperkalemia
Anemia
Early MI
Ischemic ST segment changes
LVH
Horizontal or downsloping ST segments with or without T wave inversion

ST and/or T Wave Changes Suggesting Myocardial Injury

Acute ST segment elevation with upward convexity in the leads representing the area of infarction
ST & T wave changes evolve: T waves invert before ST segments return to baseline
Associated ST depression in the noninfarct leads is common
Acute posterior wall injury often has horizontal or downsloping ST segment these same leads
Depression with upright T-waves in V₁-V₃, with or without a prominent R wave in
Note: ST & T wave changes suggesting myocardial injury can also be seen in:
Post-tachycardia sinus beats (T wave inversion)
Apical hypertrophic cardiomyopathy
Central nervous system disease

ST and/or T Wave Changes Suggesting Acute Pericarditis

Classic evolutionary pattern consists of 4 stages (but is not always present):
Stage 1: Upwardly concave ST segment elevation in almost all leads except aVR; no reciprocal ST depression in other leads except aVR
Stage 2: ST junction (J point) returns to baseline and T wave amplitude begins to decrease
Stage 3: ST waves invert
Stage 4: EGG returns to normal

Other clues to acute pericarditis:
Sinus tachycardia
PR depression early (PR elevation in aVR)
Low voltage QRS
Electrical alternans if pericardial effusion

ST and/or T Wave Changes Secondary to Intraventricular Conduction Disturbance or Hypertrophy

LVH: ST segment and T wave displacement opposite to the major QRS deflection: ST depression (upwardly concave) & T wave inversion when the QRS is mainly positive (leads I, V5, V6)
Subtle ST elevation and upright I waves when the QRS is mainly negative (leads V₁, V₂)
RVH: ST segment depression and I wave inversion in leads V₁-V₃ and sometimes in leads II, III, aVF
LBBB: ST segment and I wave displacement opposite to the major QRS deflection
RBBB: Uncomplicated RBBB has little ST displacement. I wave vector is opposite to the terminal slurred portion of QRS (upright in leads I, V₅, V₆; inverted in leads V₁, V₂)

Post-Extrasystolic T Wave Abnormality

Any alternation in contour, amplitude and/or direction of the I wave in the sinus beat(s) following an ectopic beat or beats

Isolated J Point Depression

ST segment depression ≥ 1 mm at the junction of the QRS and ST segment (J-point) lasting ≥ 0.08 seconds
Note: Most frequently seen during exercise testing.

Peaked T Waves

T wave > 6 mm in limb leads, *or*
T wave > 10 mm in precordial leads
Note: Causes of peaked I waves include:
Acute MI
Normal variant; most common in mid-precordial leads
Hyperkalemia: QT normal
Intracranial bleeding: prolonged QT; prominent U waves
LVH
LBBB

Prolonged QT Interval

Corrected QT interval (QTc) ≥ 0.42 - 0.46 seconds, *where*
 $QTc = QT \text{ interval divided by the square root of the preceding RR interval}$
Note: Be sure to measure the QT interval in a lead with a large T wave and distinct termination.

Note: QT interval varies inversely with heart rate.

Easier methods to determine QT interval:

Use 0.40 seconds as the normal QT interval for a heart rate of 70. For every 10 BPM change in heart rate above (or below) 70, subtract (or add) 0.02 seconds. (Measured value should be within ± 0.07 seconds of the calculated normal.) Example: For a HR of 100 BPM, the calculated "normal" QT interval $0.34 \pm .07$ seconds [(3 x 0.02 seconds) - 0.040 seconds]. For a HR of 50 BPM, the calculated "normal" QT interval $0.44 \pm .07$ seconds [(2 x 0.02 seconds + 0.40 seconds)].

The normal QT interval should be less than 50% of the RR interval

Note: Conditions associated with a prolonged QT interval include:

Acquired

Drugs (quinidine, procainamide, disopyramide, amiodarone, sotalol, phenothiazine, tricyclics, lithium)

Hypomagnesemia

Hypocalcemia

Marked bradyarrhythmias

Intracranial hemorrhage

Myocarditis

Mitral valve prolapse

Hypothyroidism

hypothermia

Liquid protein diets

Congenital

Romano-Ward syndrome (normal hearing)

Jervell and Lange-Nielson syndrome (deafness)

Prominent U Waves

Amplitude of 1.5 mm

Note: The U wave is normally 5-25% the height of the T wave, and is largest in leads V_2 and V_3

Note: Causes include:

Hypokalemia

Bradyarrhythmias

Hypothermia

LVH

Organic heart disease

Drugs (digitalis, quinidine, amiodarone, isoproterenol)

16.16 Pacemaker Function and Rhythm

Atrial or Coronary Sinus Pacing

Pacemaker stimulus followed by an atrial depolarization

Ventricular Demand Pacing

Pacemaker stimulus followed by a QRS complex of different morphology than intrinsic QRS

Must demonstrate inhibition of pacemaker output in response to intrinsic QRS

AV Sequential Pacing

Atrial followed by ventricular pacing

Could be DVI, DDD, DDI, or DOG pacing mode

Ventricular Pacing, Fixed Rate (Asynchronous)

Ventricular pacing with no demonstrable output inhibition by intrinsic QRS complexes

Dual Chamber, Atrial-Sensing Pacemaker

For atrial sensing, need to demonstrate inhibition of atrial output and/or triggering of ventricular stimulus in response to intrinsic atrial depolarization

DDD and possibly VAT or VDD

Pacemaker Malfunction, not Constantly Capturing (Atrium or Ventricle)

Failure of pacemaker stimulus to be followed by depolarization

Note: Rule out “pseudo-malfunction” (i.e., pacer stimulus falls into refractory period of ventricle)

Pacemaker Malfunction, not Constantly Sensing (Atrium or Ventricle)

Pacemakers in Inhibited Mode: Failure of pacemaker to be inhibited by an appropriate intrinsic depolarization

Pacemakers in Triggered Mode: Failure of pacemaker to be triggered by an appropriate intrinsic depolarization

Note: Watch for “pseudo-malfunction” (i.e., pacer stimulus falls into refractory period of ventricle)

Note: Premature depolarizations may not be sensed if they:

Fall within the programmed refractory period of the pacemaker

Have insufficient amplitude at the sensing electrode site

Note: Any stimulus falling within the QRS complex probably does not represent sensing malfunction (commonly seen with right ventricular electrodes in RBBB).

Pacemaker malfunction, not firing

Failure of appropriate pacemaker output

Pacemaker malfunction, slowing

Increase in stimulus intervals over the programmed intervals

Note: Usually an indicator of battery end of life

Note: Often noted first during magnet application

16.17 Suggested or Probable Clinical Disorders

Digitalis Effect

Sagging ST segment depression with upward concavity

T wave flat, inverted, or biphasic

QT interval shortened

U wave amplitude increased

PR interval lengthened

Note: ST changes are difficult to interpret in the setting of LVH, RVH, or bundle branch block. However, if typical sagging ST segments are present and the QT interval is shortened, consider digitalis effect.

Digitalis Toxicity

Digitalis toxicity can cause almost any type of cardiac dysrhythmia or conduction disturbance except bundle branch block. Typical abnormalities include:

Paroxysmal atrial tachycardia with block.

Atrial fibrillation with complete heart block (regular RR intervals).

Second or third-degree AV block.

Complete heart block with accelerated junctional rhythm or accelerated idioventricular rhythm)

Supraventricular tachycardia with alternating bundle branch block

Antiarrhythmic Drug Effect

Prolonged QT interval

Prominent U waves (one of the earliest findings)

Advanced cases have biventricular hypertrophy

Note: Primum ASDs represent 15% of all ASDs, and are due to deficient tissue in the lower portion of the septum. These ASDs are usually large, may be accompanied by anomalous pulmonary venous drainage, and are associated with a cleft anterior mitral valve leaflet, mitral regurgitation, and Down's syndrome.

Dextrocardia, Mirror Image

Suggested by the following:

P-QRS-T in leads aVL and I are inverted or "upside down"

Decreasing R wave amplitude from leads V₁-V₆

Note: Dextrocardia and lead reversal can both produce an upside down PQRST in leads I and aVL. To distinguish between these conditions, look at the R wave pattern in V₁-V₂:

Reverse R wave progression suggests dextrocardia

Normal R wave progression suggests lead reversal

Mitral Valve Disease

Mitral Stenosis

Combination of right ventricular hypertrophy and left atrial abnormality is suggestive

Mitral valve prolapse

flattened or inverted T waves in leads H, III and aVF (and sometimes in right precordial leads) ± ST segment depression, which is sometimes present in the left precordial leads

Prominent U waves

Prolonged QT interval

Chronic Lung Disease

Suggested by any of the following:

Right ventricular hypertrophy

Right axis deviation

Right atrial abnormality

Shift of transitional zone clockwise (poor R wave progression)

Low voltage QRS

Pseudo-anteroseptal infarct pattern (low anterior forces)

S waves in leads I, II, and III (S₁ S₂ S₃ pattern)

May also see sinus tachycardia , junctional rhythm , various degrees of AV block, IVCD, and bundle branch block,

ST and/or T wave changes secondary to ventricular hypertrophy or conduction abnormalities

Apical variant of hypertrophic cardiomyopathy has deep T wave inversions in V₄-V₆

Left axis deviation in 20%

Coronary Artery Disease

Use only when definitive evidence of myocardial injury or infarction is present

Central Nervous System Disorder

“Classic changes” usually in precordial leads

Large upright or deeply inverted I waves

Prolonged QT interval (often marked)

Prominent U waves

Other changes:

T wave notching with loss of amplitude

ST segment changes:

Diffuse ST elevation mimicking acute pericarditis, *or*

Focal ST elevation mimicking acute myocardial injury, *or*

ST depression

Abnormal Q waves mimicking MI

Almost any rhythm abnormality (sinus tachycardia or bradycardia, junctional rhythm, VPCs, ventricular tachycardia, etc.)

Note: EGG findings in CNS disease can mimic those of:

Acute MI

Acute pericarditis

Drug effect or toxicity

Myxedema

Low QRS voltage in all leads

Sinus bradycardia
T wave flattened or inverted
PR interval may be prolonged
Frequently associated with pericardial effusion
Electrical alternans may occur
Hypothermia
Sinus bradycardia
PR, QRS, and QT prolonged
Osborne (“J”) wave: late upright terminal deflection of QRS complex (“camel hump” sign); amplitude increases as temperature declines -
Atrial fibrillation in 50-60%
Other arrhythmias include AV junctional rhythm, ventricular tachycardia, ventricular fibrillation

Sick Sinus Syndrome

One or more of the following:

Marked sinus bradycardia

Sinus arrest or sinoatrial exit block

Bradycardia alternating with tachycardia

Atrial fibrillation with slow ventricular response preceded or followed by sinus bradycardia, sinus arrest, or sinoatrial exit block

Prolonged sinus node recovery time after atrial premature complex or atrial tachyarrhythmias

AV junctional escape rhythm

Additional conduction system disease is often present, including AV block, IVCD, and/or bundle branch block.

16.18 Transmitting Data

The ECG Core Lab will periodically electronically transmit ECG data to the Data Coordinating Center. Data will include all ECG items from the AASK Trial ECG Form 114 and other items.

CHAPTER 17. QUALITY CONTROL

17.1 Quality Control Introduction

In addition to the quality control methods and programs routinely used at clinical center laboratories and central laboratories, quality control mechanisms for the AASK Cohort Study are outlined in the following sections and elsewhere in the AASK Cohort Protocol and this AASK Cohort Manual of Operations.

17.2 Quality Control of Clinical Centers

Investigators

No specific training and certification measures are required for Principal Investigators and Co-Investigators unless they are responsible for performing study measurements or procedures. All investigators are expected to be actively involved in study activities at their center, in study-wide committees (as assigned), and in meetings of the Steering Committee. Any investigator who measures blood pressure must be initially trained and certified and must keep his/her certification up to date.

Study Coordinators

No specific training and certification measures are required for study coordinators. Annual training sessions will be held to update personnel on protocol procedures and requirements. However, any study coordinator who measures blood pressure must be initially trained using training tapes and must be certified and must keep his/her certification up to date. This is described in "Blood Pressure Measurement" Chapter 6 of this Manual of Operations.

Data Entry Specialist

Data entry personnel do not require special training for data entry.

Clinical Center

Each clinical center is to be certified in use of the ABPM device. This is described in "Clinical Center Data Collection and Processing ABPM Information for the CVD Core Laboratory" Chapter 13 of this Manual of Operations.

17.3 Genetics Core Laboratory

Quality control procedures carried out within the genetics core laboratory are described in "Specimen Processing and Storage at the Genetics Core Laboratory" Chapter 8 of this Manual of Operations.

17.4 Biochemistry Laboratory

The Central Biochemistry Laboratory has an internal quality control system that was established prior to analyzing any AASK or AASK Cohort samples. This system will be outlined in the Manual of Operations for the Central Biochemistry Laboratory(s) which is prepared and submitted by the Central Laboratory to the DCC prior to initiating the study.

This system includes:

- 1) The inclusion of at least two known quality control samples; the reported measurements of the quality control samples must fall within specified ranges in order to be certified as acceptable.
- 2) Calibration at FDA approved manufacturers' recommended schedules.

Detailed information on quality control procedures carried out within the Central Biochemistry Laboratory are described in "Central Biochemistry Laboratory Sample Collection and Handling" Chapter 10 of this Manual of Operations.

17.5 Cardiovascular Core Laboratory

Quality control procedures carried out within the Cardiovascular Core Laboratory for ECHO, ABPM, and ECG are described in Manual of Operations Chapters 12, 14, and 16, respectively.

17.6 Data Forms and Data

In the AASK Cohort Study, each clinical center's staff members will enter all Clinical Center data electronically. Appropriate edit checks will be in place at the key entry (database) level. Original study forms will be entered and kept on file at the Clinical Center. A subset will be requested later for quality control; when a form is selected, the Clinical Center staff will pull that form, copy it, and send the copy to the DCC for review and data entry.

Any and all paper forms or copies of forms (i.e., copies of ECG strips, questionnaires) that pertain to the AASK study are to be filed in the participant's file in a logical and consistent manner to provide accessibility for the duration of the study. Participant files are to be stored in numerical order and stored in a secure and accessible place and manner. Participant files will be maintained in storage for a period of 3 years after completion of the study.

17.7 Site Visits of Clinical Centers, Central Facilities, and the DCC

Site visits will be made to Clinical Centers when needed. The primary goals of the site visits are: 1) to observe the clinic under normal operating conditions for adherence to protocol; 2) to increase/improve communication between the study administration, the clinic personnel and the DCC; and 3) to demonstrate the study's concern for the quality of data collection. Site visit teams consist of a DCC staff member familiar with the AASK protocol and requirements, and an NIH representative. A Study Coordinator from another clinical center may be included. All site visits teams will compile a report that is given to the Clinical Center PI and to the DCC. These reports are reviewed by the AASK Cohort Chairs Subcommittee and the Steering Committee.

Site visits of the Central Biochemistry Laboratory, the Genetics Core Laboratory, and the Cardiovascular Core Laboratory will be done as needed.

A special committee may be formed to site visit the DCC. The exact membership of this committee would be determined by NIDDK. It is expected to include a representative from NIDDK, representatives from one or more of the Clinical Centers, a representative from the External Advisory Committee, a biostatistician, and an epidemiologist with expertise in cohort studies.

17.8 Quality Control of the Data Coordinating Center

17.8.1 Paper Forms

Any and all paper forms or copies of forms (i.e., cardiovascular hospitalization discharge summaries) that pertain to the AASK study will be filed in a logical and consistent manner in the participant's file at the DCC. Participant files will be stored in numerical order and stored in a secure and accessible place and manner.

17.8.2 Participant Recruitment/Enrollment

The Data Coordinating Center will produce summary enrollment reports weekly and detailed reports monthly. Enrollment reports will include the number of patients not yet on dialysis that have enrolled in the cohort study and the number of patients already on dialysis. These reports will become part of the AASK Cohort Study Weekly Report. These reports will be verified by each clinical center and discrepancies reported to the DCC.

17.8.3 Data Transmission and Editing

The data entry screens will resemble the paper forms approved by the Steering Committee. Data integrity will be enforced through a variety of mechanisms. Referential data rules, valid values, range checks, and consistency checks against data already stored in the database (i.e., longitudinal checks) will be supported. The option to choose a value from a list of valid codes and a description of what each code means will be available where applicable. Checks will be applied at the time of data entry into a specific field and/or before the data is written (committed) to the database. Modifications to data written to the database will be documented through either the data change system or an inquiry system. Data entered into the data base will be retrievable for viewing through the data entry applications. The type of activity that an individual user may undertake is regulated by the privileges associated with his/her user identification code and password.

17.8.4 Data Discrepancy Inquiries and Reports to Clinical Centers

Additional errors will be detected by programs designed to detect missing data or specific errors in the data. These errors will be summarized along with detailed descriptions for each specific problem in Data Query Reports that will be sent to the Clinical Centers via e-mail. Reports regarding the length of time required to resolve queries as well as reports indicating

those centers and their specific queries that are still open will be prepared monthly.

The Clinical Center study coordinator will respond by checking the original forms for inconsistency, checking other sources to determine the correction, modifying the original (paper) form entering a response to the query. Note that it will be necessary for the Clinical Centers to respond to each query in order to obtain closure on the queried item.

The Clinical Center personnel will be responsible for making appropriate corrections to the original paper forms whenever any data item is changed. No data revisions will be made over the telephone. Written documentation of changes will be available via electronic logs and audit trails.

Feedback to the Clinical Centers will occur at various times depending upon the specific information being disseminated. Most reports will be distributed over electronic mail. Clinical Centers will receive recruitment and retention and missing forms reports.

Biochemistry reports will be sent via e-mail when data are received from the Central Lab.

Monthly reports summarizing subject enrollment, retention, patient compliance, clinic performance, and progress will be sent to the Clinical Centers, the Central Labs, and the NIH Project Office.

Missed Visit Reports will be provided to each Clinical Center monthly specifying patients completing and missing scheduled visits at that Center. This report should enhance the completion of follow-up visits.

Missing Query Response Reports will be provided to each Clinical Center monthly and will consist of queries that have been identified by the DCC and have not yet been responded to by the Clinical Center. These will highlight any query requests that are over 14 days delinquent.

Missing Forms Reports will show missing forms for clinical centers and central facilities.

17.9 Security and Back-Up of Data

The need for strict confidentiality of all study records will be emphasized to the staff of the DCC. All forms, diskettes and tapes related to study data will be kept in locked cabinets. Access to the study data will be restricted. In addition, Clinical Centers will only have access to their own center's data. A password system will be utilized to control access to all computer accounts as well as database accounts. These passwords will be changed on a regular basis. All reports prepared by the DCC will be prepared such that no individual subject can be identified.

A complete back-up of the primary DCC database will be performed twice a month. These tapes will be stored off-site in a climate controlled facility and will be retained indefinitely. Incremental data back-ups will be performed on a daily basis. These tapes will be retained for

at least one week on-site. Back-ups of periodic data analysis files will also be kept. These tapes will be retained at the off-site location until the Study is completed and the database is on file with NIH. In addition to the system back-ups, additional measures will be taken to back-up and export the database on a regular basis at the database management level. The Oracle database management system provides extensive back-up and documentation.

17.10 Reporting Study Results

All reports for external distribution (e.g., manuscripts) will be prepared in duplicate and reviewed by the DCC Director or Deputy Director. All files, programs and data sets will be archived. See the Section on Maintenance and Disposition of Study Documents, Data and Materials for more details.

17.11 DCC Database Software

The AASK Cohort Study database is in Oracle. Oracle is an American National Standards Institute (ANSI) compliant relational data base management system that operates across platforms. It is a premier database product on the Sun workstation environment. The Oracle products in use at the Cleveland Clinic's Department of Biostatistics and Epidemiology include the web, forms and report. All Oracle software for this study is running at the version 8.1.7 release level.

Oracle, coupled with the hardware available within the department, is well suited for the development of large databases with sophisticated data integrity checks. The connectivity of the computer system allows data entry to occur from workstations within the department or from a "remote" site. Oracle supports a graphical user interface mode (GUI) as well as a character based environment. Thus, access to the Oracle data base is possible from many different types of terminals ranging from character based to a graphical based terminal and, therefore, is not restricted to a particular type of hardware or software interface.

Oracle facilitates sophisticated integrity checks through a variety of mechanisms including stored procedures, stored triggers, and declarative database integrity--for between table verifications. Oracle allows data checks to be programmed once in the database rather than repeating the same checks among many applications. Oracle provides multi-user support, ANSI standard SQL, journaling for database recovery and database transaction rollback. Security is enforced through passwords and may be assigned at different levels to groups and individuals. A query optimizer automatically selects the most efficient way for performing all database transactions. Oracle provides a utility that allows for bulk loading data into the database while enforcing any integrity checks previously defined in the database. This feature will be useful in loading the central lab data that will be electronically output from the labs computerized analyzers. Additionally, Oracle is compatible (via SAS access) with the SAS system that will be the primary statistical analysis tool.

17.12 DCC Data Analysis Software

SAS is the predominant analysis tool and has a very solid reputation within the field of statistical analysis. In addition to the base SAS product, several add-on features are available including: SAS/STAT, SAS/GRAPH, SAS/IML. All are necessary to run currently developed analyses and for the development of future analyses. Means for importing/exporting SAS data from/to other platforms are provided.

SAS/ACCESS software provides an interface between the SAS System and the ORACLE database management system by directly accessing data in ORACLE tables using a SAS program.

S-Plus is available within the department and is used primarily for sophisticated data modelling. Its interactive graphics capabilities make it a superior product and allow it to contribute significantly to the types of analyses that are able to be conducted. It is an excellent tool for programming new statistical methods because of its extensive selection of mathematical and array manipulation routines.

The Biomedical Computer Program P-Series (BMDP) package is accessible to the Department via the Medical Information Services Division's DEC VAX. BMDP provides specialized programs for categorical data analyses, logistic regression, proportional hazards modelling, and analysis of longitudinal and incomplete repeated measures data.

CHAPTER 18. COMPUTING AND DATA ENTRY

18.1 Computing Systems Overview

Computing for AASK can be divided into two broad areas: computing at the Clinical Centers or Central Labs, and computing at Data Coordinating Center (DCC). The purpose of this overview is to describe in general terms how these systems are organized.

Each Clinical Center has a personal computer. These PC's will be used, for study purposes, to run software for communicating over the Internet to the DCC. They may additionally be used for a variety of tasks useful for the centers' work related to the study, such as word processing.

To connect from your PC to the DCC (located in Cleveland, Ohio, at the Cleveland Clinic Foundation), you will be making use of the Internet, a world-wide network of computers, composed of and supported by primarily academic, governmental, and non-profit institutions. Using the Internet, you will be able to interact with the DCC's computers in Cleveland.

The PC that sits in your office is not directly connected to the Internet. You must first connect from your PC to a nearby computer that is on the Internet, and then from that computer to the DCC. This nearby computer is called an Internet "node." Just what kind of computer each center will connect to in order to access the Internet will vary from center to center. Some centers will be connected to computers at their institution that are an Internet node. This connection might be through a campus network, or it might involve dialing up the institution's computer over a phone line using a modem. Other centers will be utilizing a public provider of Internet access for a small monthly fee. Connecting to such a service will involve making a local phone call to connect using a modem. In either case, this manual will refer to the nearby computer to which the AASK center's personal computer connects to gain Internet access as the Local Internet Provider (LIP).

The DCC's computer is also connected to the Internet. Hence, connecting from your personal computer to your LIP allows you to reach the DCC across the Internet. In fact, you'll be using the DCC's computer directly when you enter data, and receive reports and mail messages from the DCC.

18.2 Your AASK Study Personal Computer

Each center is required to have a minimum of one PC dedicated to the purposes of the AASK Study. The DCC's recommended specifications for your PC are as follows:

PC Specification

A 500 Mhz or better

Monitor

Color monitor.

Internet Connection

A live connection to the Internet.

Browser Software

Netscape Communicator 4.77 or Internet Explorer 5.5 or higher. Adobe Acrobat Reader 4.05. Oracle Jinitiator 1.1.8.14. These can be downloaded from the DCC's website as specified in Appendix A.

18.3 Accessing the DCC Website to Enter Data

See Appendix A for instructions on how to set up your PC to access the DCC's website.

After you have successfully entered the website, you will see a menu titled "AASK Study". At this point, resize the window to the largest that will fit on the screen for optimal viewing. You can then choose a form or report from the menu, or you can go to the "Query" menu to answer or view your queries.

18.4 Passwords

You will have a web username and password and an Oracle database username and password. The usernames should be the same for both: First initial of your first name followed by the first seven characters of your last name. Please do not share passwords. Passwords will need to be changed every 75 days. Passwords are not case sensitive.

18.4.1 Selecting a Good Password

Here are some good references for picking a good password:

http://www.net.berkeley.edu/dcms/faq/good_pw.html

<http://www.msc.tamu.edu/services/cops/security/goodpasswd.html> and

<http://www.cs.umd.edu/faq/Passwords.shtml>

Please read them all as they all have good advice.

18.4.2 Changing Your Password

There is a menu option available to change your password.

18.5 **Instructions: How to Enter Study Data into the Database**

Press enter, tab or click your mouse to move from field to field within a form. Note that you will see bubble help when you move your mouse over the top buttons. The upper left button should be the save button. When you are finished entering data for a form, click on the save button, or choose “Save” from the “Action” menu, or press the F10 (Accept or Commit) function key. The F10 key corresponds to the Oracle function “Accept” or “Commit”. You will see a message at the bottom of the screen indicating how many new records were added to the database. You can get out of a form by pressing the “Exit” button or choosing “Exit” from the “Action” menu. There is also a speed key for this. If you want to enter another form you should navigate to the top of the form, and press the “Insert Record” button. “Insert” can be selected from the “Record” menu. Unfortunately, you are not permitted to remove records once you have saved/committed them. You will need to send the DCC a query to do that. You are also not permitted to change certain key fields or fields that determine eligibility. Again, you will need to send a query to the DCC.

18.5.1 Key mappings

Ctrl+F1 means hold down the <Ctrl> key and then simultaneously press the <F1> key. Now release <F1> and then <Ctrl>. Another way to get to the key mappings is to choose “Keys” from the “Help” menu.

18.5.2 List of Values (LOV)

Note that you may see messages on the bottom of your screen. If you see “List of Values”, that means you can choose “Display List” from the “Edit” menu, or press F9 to retrieve a list of values to your screen which you can scroll through and make a selection.

18.5.3 Editing

If the field is smaller than the text you are typing into it, you can choose “Edit” from the “Edit” menu, or press Ctrl+E when your cursor is in that field. This will open up a pop-up box containing a larger view of that field. Use this also for viewing.

18.5.4 Navigation

Other useful Oracle functions that you can use are “Next Record” and “Previous Record”. You can find buttons and speed keys for these and they are also on the “Record” menu. Use these to navigate between forms or detail records (for example, in medication forms).

18.5.5 Error Messages

If you skip over a required field, you will see the error message:

Field must be entered.

If you enter a value that is not possible for that field, you will see the error message:

Invalid value for field name.

If you enter a non-numeric character in a numeric field, you will see the error message:

Legal characters are 0-9 - + E.

If you try to update previously entered data without using the [Change Value] button, you will see:

Field is protected against update.

You will also see other various error messages as well. If you can't figure out why you are getting that particular error message, please write down the complete message, and also choose Help->Display Error while the message is on the screen to see if a further explanation pops up before calling us. If you get stuck, it may help to use Cancel Query or Query->Cancel (if you see "Enter-Query" on the bottom of your screen), Action->Clear All or Record->Clear

18.6 Instructions: How to Change Study Data in the Database

18.6.1 Retrieving Data

Once the data has been entered, you can retrieve it to your screen for viewing:

- Access the form # you want to view.
- Press the [Enter Query] key or button.
Note the hint line will say "Enter-Query".
- Enter the Patient ID and visit number.
Visit number may not be applicable.
- Press the [Execute Query] key or button.

18.6.2 Real-Time Changes

Clinical Center change to data within 7 days and the new value is acceptable to the database:

- Query the data from the appropriate form.
- Position cursor on field to be changed, and then press the [Change Value] button.
- Type in the new value.
- Assuming the value passes all edit checks, when you leave that field your change will be committed to the database, and you will receive a data change number.
- If the change does not pass the edit checks, change the value back to the original value, and then you will get a popup box that will ask you if you want to send a query to the DCC.

18.6.3 Data Change Within 7 Days But The Database Will Not Accept It

- Retrieve the data.
- Put the cursor on that field.
- Press the [Change Value] button.
- Press [Enter] only.
- A pop-up box will appear.
- Answer “OK” to the popup box.
- A new screen will appear that will allow you to enter a requested value and an explanation.
- You will receive an inquiry number after you save the request. You can use this number to check to see if the DCC signed off on your inquiry.
- After investigating, the DCC will take the appropriate action, and then use the DCC Sign-Off screen to indicate the final status of the request.
- A “DCC Sign-Off to CC Initiated Data Inquiry” will be sent to the DCC and CC.
- No further action is required.

18.6.4 Clinical Center Change to Data After 7 Days

- Retrieve the verified data.
- Position the cursor on the field to be changed.
- Press the [Change Value] button.
- A new screen will appear that will allow you to enter a requested value and an explanation.
- Enter the new value as well as text describing the desired change. The DCC will use this response to investigate the request.
- You will receive an inquiry number after you save the request. You can use this number to check to see if the DCC signed off on your inquiry.
- The DCC will take the appropriate action, and then use the DCC Sign-Off screen to indicate the final status of the request.
- A “DCC Sign-Off to CC Initiated Data Inquiry” will be sent to the DCC and CC.
- No further action is required.

18.7 Instructions: How to Initiate and Respond to Queries

18.7.1 Clinical Center Initiation of Queries

Queries can be initiated by the Clinical Center as described in the above section on changing data.

18.7.2 Clinical Center Response to a DCC Initiated Inquiry

- You will receive a DCC initiated inquiry report through e-mail, or you can go to the “Query” menu and choose “Respond to a DCC Initiated Inquiry” to find unanswered queries.

- When the screen appears you can press [Execute Query] to retrieve all unanswered queries, or press [Enter Query] and enter the query # and then press [Execute Query].
- If you do not enter an inquiry number, all unanswered queries will be retrieved. You need to press [Next Record] to navigate to the other queries. Keep pressing [Previous Record] to get back to a previous query.
- Position your cursor on the "DCC text" field".
- Choose Edit->Edit if you want to read the entire explanation from the DCC as to why you are being queried.
- Navigate to "New Value".
- Type a new value for the field being inquired. If a different field requires changing, leave it blank or enter N/A for not applicable.
- Navigate to "CC text", and enter an explanation for your value. This field must be answered in order for the DCC to take action. Please make sure that your explanation is specific and complete.
- The explanation can be up to 2000 characters. Click on the [Save and Exit] button on the bottom of the screen to save the text. Click on [Exit and Don't Save] if you do NOT want to save the text.
- The DCC will then make the appropriate updates to the database.
- It is very important that the CC respond within 3 business days.

18.8 E-mail Alias Lists

From your center's aaskxxxx study account at the DCC, you will have access to several pre-defined distribution lists. These include:

aaskall@bio.ri.cc.org - lists every known e-mail address for any AASK study participants including the clinical centers, central labs, drug companies, NIH personnel, committee members, etc.

aask_cc@bio.ri.ccf.org - lists all 20 clinical centers, plus the DCC

aaskdcc@bio.ri.ccf.org - lists all DCC members

ac-system@bio.ri.ccf.org - lists the programming staff at the DCC

18.9 Retrieving Data from Forms

18.9.1 Introduction

Data can be retrieved in several ways from the form application. In order to "query" data available in the database for the information on a given form application, the [Enter Query] and [Execute Query] keys can be used. The screen will be populated with the first set of patient data for the form application being accessed. By pressing the [next record] or [previous record] keys, you will have the ability to view the next or previous set of data.

There are different ways to retrieve data. You can execute simple queries that meet specific criteria, as well as complex queries that satisfy several conditions. The following topics are discussed.

- Matching exact values
- Entering variable conditions
- Matching values that meet a specified pattern

18.9.2 Matching Exact Values

Suppose you want to check on all instances of visits of the 'FV' type for a given patient ID (010001 for example). The data entry screens can retrieve the record(s) that contains specifically these values. The following are general steps for retrieving records that match exact values:

- 1) Access the appropriate form via the menu system.
- 2) Press [Enter Query]
- 3) Type the values you want to match into the appropriate fields.
For this example, cursor to the Patient ID field and type 010001.
- 4) Press [Execute Query]
- 5) Press [Next Record] or [Previous Record] to view the retrieved data.

NOTE: If there is not any data that meets the specified criteria, the following message will be displayed on the status line of your screen:

"FRM-40301: Query caused no records to be retrieved. Re-enter."

18.9.3 Entering Variable Conditions

Sometimes it is not practical to enter the exact values that you want retrieved data to match. For example, you might want to retrieve the following:

- All Form 111's with visit type = FV and visit number >6
- All Form 111's after 04/19/2002

Rather than entering an exact data value, you can enter a relational operator before the data values in one or more fields.

The following table shows some relational operators typically used:

<u>Operator</u>	<u>Meaning</u>	<u>Example</u>
=	equal to	= '01/01/2002'
!=	not equal to	!=6
>	greater than	>6
>=	greater than or equal to	>=6

<	less than	<6
<=	less than or equal to	<=6

For example, to select data that have a visit number >6, press [Enter Query] and type >6 on visit number field and press [Execute Query]. To select any Form 111's after 04/19/2002, press [Enter Query], type >=04/19/2002, and press [Execute Query].

18.9.4 Using Pattern Matching

Pattern matching provides the capability to fetch data where a value for a field fits a certain pattern. This is useful when specifying search criteria on "string" or character value fields.

When specifying a pattern "_" represents any single character and "%" represents any combination of characters. The "_" and "%" symbols are referred to as wild cards.

For instance, suppose you are interested in all NDC codes in the Drug database that have the medication CATAPRES listed in the name of the medication.

- 1) Access the Drug database via the Form 140 data entry screen.
- 2) Retrieve the medication data for a specific patient.
- 3) Place your cursor on a blank NDC field.
- 4) Press the [List] key. You will be presented with a blank screen titled "Current Drug Pricing Database." Notice that you are already in "Enter Query" mode.
- 5) Place the cursor on the field labelled "BRAND NAME:"
- 6) Type %CATAPRES%.
- 7) Press [Execute Query] key.
- 8) Press the [Next Record], [Previous Record] keys to view the retrieved data.

To further refine the search, for all Catapres medications with TTS in the label, restart the process by pressing [Enter Query], type \$CATAPRES%TTS% in the Brand name field, press [Execute Query}.

18.9.5 Count Query Hits

If you are interest in simply a count of how many records meet your search criteria, press the [Count Query Hits] key in place of the [Execute Query] key. Rather than having a screen full of data returned to your screen, you will receive a message indicating the number of "records" that meet the search criteria. Using the Catapres example above, if you search on %CATAPRES%TTS%, with the [Count Query Hits] key, you will receive the message:

"FRM-40355: Query will retrieve 3 records"

This function can be helpful if you are interested in determining a count of patients that meets some specific criteria. For instance, suppose you are interested in knowing how many patients have been seen at some other outpatient clinical location on the Visit/Missed Visit Form 111. Access Form 111 from the menu. Cursor to the Patient ID field. Press [Enter

Query]. Cursor to item #5c. Type a value of 2 for the field. Press the [Count Query Hits] key.

Notes:

- Queries can be issued in the first block of multi-block forms.
- Queries cannot be specified on namecode. This is a lookup field and thus not searchable.

Appendix A

AASK Cohort Study Website

Web Site Downloadable Utilities

The website <https://clinapps.bio.ri.ccf.org/download.html/> contains a number of files needed to fully utilize the AASK Consortium web application.

Included are:

- (1) Netscape Communicator version 4.77 cc32d477.exe
- (2) Adobe Acrobat Reader version 4.05 rs405eng.exe
- (3) Oracle JInitiator version 1.1.8.14 jinit11814.exe

The following steps must be performed in the order given below:

- 1) If you do not have Netscape 4.77 already installed, install it by double-clicking on cc32d477.exe. This is the latest version in the 4.x series. We've seen numerous problems with the 6.x Netscape and do not recommend it at this time.
- 2) Double-click jinit11814.exe to install (accept all defaults). This is a thoroughly debugged and Oracle-certified version of Sun Microsystems's Java Plug-In which replaces the browser's built-in Java Virtual Machine when the AASK application is run.

Once these components are installed:

Please go to <https://clinapps.bio.ri.ccf.org/> and follow the links to AASK and then log in to the test system.

NOTE: Using Netscape 6.x and Jinitiator

Aside from other directions in the computing section of the MOP and the above, the user still might not be able to run the application and gets the message to 'Get Plug-In' even after JInitiator had been installed. The problem is that the plug-in, NPJinit-11814.dll, may not have been copied to the correct directory. It needs to be in the Netscape Plug-Ins directory along with other Java dlls. This seems particularly true for Netscape 6 and higher especially if there is a previous version of Netscape installed. To do to this, use the Windows 'Search' or 'Find' utility (Depends on which version of Windows OS). Once you have located 'NPJinit-11814.dll' copy it to the Plug-Ins directory under the current version of Netscape if it isn't there already.

Appendix B

Key Mapping

FUNCTION	KEY
Block Menu	F5
Clear Block	Shift+F5
Clear Field	Ctrl+U
Clear Form	Shift+F7
Clear Record	Shift+F4
Commit	F10
Count Query	Shift+F2
Delete Record	Shift+F6
Display Error	Shift+F1
Down	Ctrl+L or Down
Duplicate Item	F3
Duplicate Record	F4
Edit	Ctrl+E
Enter Query	F7
Execute Query	F8
Exit	Ctrl+Q
Help	Ctrl+H or F1
Insert Record	F6
List of Values	F9
List Tab Pages	F2
Next Block	Ctrl+PageDown
Next Field	Tab
Next Page	PageDown or F12
Next Primary Key	Shift+F3
Next Set of Records	Shift+Ctrl+PageDown
Previous Block	Ctrl+PageUp
Previous Field	Shift+Tab
Previous Page	PageUp or F11
Print	Shift+F8
Return	Return
Scroll Down	Shift+Down
Scroll Up	Shift+Up
Show Keys	Ctrl+F1
Up	Ctrl+P or Up
Update Record	Ctrl+U

CHAPTER 19. COLLECTION OF FINGERNAIL CLIPPINGS IN THE AASK COHORT STUDY

19.1 Background

Acute exposure to high levels of some heavy metals is known to be nephrotoxic. However, the effects of chronic exposure to lower levels of such metals on renal function are unclear. Several biomarkers are potentially available for measuring heavy metal exposure in large epidemiologic studies, including serum, urine, hair and fingernails. We propose the use of fingernails in the AASK cohort study because of the availability of long-term reliability data because handling of the samples is easier and may be less subject to contamination, and because of the availability of instrumental neutron activation analysis. Fingernail heavy metal levels have been extensively used and validated for several trace elements, such as selenium and arsenic, and are being increasingly used for mercury, iron, copper, and zinc.

19.2 Data Collection Schedule

Data collection of fingernail clippings will occur at baseline and annually for the duration of the AASK cohort study.

19.3 Overview of Data Collection Procedures

19.3.1 Study Materials

Each clinic site will be provided with the following study materials:

Instructions for the participant

These instructions will guide the participant through the data collection process.

Self-administered data collection form

This form contains questions regarding the type of nail clippings provided (fingernail or toenail).

Small plastic bag to collect the nail clippings

These bags should be made of polyethylene, clear, approximately 1.5”w x 2”h, minimum thickness of 2 mil and have a reclosable seal. Note: some Ziploc style bags have a colored seal - these are not acceptable. These small bags are provided to each clinical center. You will need to contact the DCC if additional bags are needed.

Nail clippers

The nail clippers used must be 100% stainless steel to prevent metal contamination of the nail clippings.

19.3.2 Instructions for Data Collection

If possible, participants should be asked to refrain from cutting their fingernails prior to the visit and to avoid wearing nail polish. There is no preparation, including hand washing, that is required prior to nail clipping. Each participant will clip his/her fingernails according to the instructions provided and empty the nail clippings into the small, plastic bag provided. Whenever possible, participants should clip all ten (10) fingernails, removing approximately 1 millimeter from each nail. This amount will allow for accurate determination of heavy metal content during analysis. Participants should only use the nail clippers that are provided, because they are specifically designed to minimize contamination of the nail clippings.

Collection of fingernails is preferred. Fingernails and toenails should not be collected in the same plastic bag; the participant must choose one or the other. It is recommended that the participant clip his/her fingernails at the clinic visit. However, if the participant cannot provide fingernail clippings, he/she may either clip his/her toenails instead, or may clip his/her fingernails from home at a later date.

If the participant has his/her nails cut by a doctor, podiatrist, manicurist, etc., the participant may take the nail clippers and plastic collection bag with them to their next visit. If the participant intends to provide clippings at a later date, he/she will be provided with a self-addressed stamped envelope to mail the clippings back to the AASK clinical center. The cost of the self-addressed envelopes will be the responsibility of the AASK clinical center.

After clipping their fingernails, participants will then fill out the self-administered data collection form. The data collection form and plastic bag containing nail clippings should be labeled by the clinic staff with the date of visit, participant ID and the date the nails were collected (if different from the visit date) according to AASK standards, no other identification data will be used. The collection bag should also be labeled with the ID number and collection date. Participants may keep the nail clippers that were provided, however, they should be asked to save these nail clippers to be used for subsequent annual data collection visits.

19.4 **Storage of Nail Clippings**

The small plastic bags containing the nail clippings will be stored at room temperature in a dry environment at each clinical center. Each clinical center will ship the collected nail clippings along with a copy of Form 168 directly to the AASK central laboratory for storage at intervals designated by the AASK Cohort Coordinating Center.

19.5 **Analysis of Nail Clippings**

Procedures for nail clipping analyses are dependent upon identification of requisite funding. A convenient option will be to use the Laboratory for Instrumental Neutron Activation Analysis, part of the Interfaculty Reactor Institute of the Delft University of

Technology (The Netherlands), a research nuclear reactor at which neutron activation analysis will be performed. This facility has extensive experience in performing this type of analysis for large epidemiologic studies.

19.6 Eligibility Criteria

19.6.1 Nail Treatments

Nail Polish

We prefer it if the participants do not wear nail polish on the data collection visit, however, painted nail clippings will be accepted.

Acrylic Nails

Acrylic nails are not acceptable. The participant should be asked to provide toenail clippings instead.

Other nail treatments (nail glue, nail strengtheners)

These are acceptable.

19.6.2 Miscellaneous Concerns

Participant cannot clip nails by themselves

If the participant has his/her nails clipped by a doctor, podiatrist, etc., the participant may take the clippers and collection bag to their next visit.

The participant has nail fungus or discoloration

The participant may still participate as long as the procedure does not cause pain or discomfort.

The participant cannot clip all ten nails

The participant should be asked to clip as many nails as possible. If the participant has very short fingernails and cannot clip at least one millimeter, we would prefer they take the clippings at home when the nails have had a chance to grow. If the participant has a few long nails, they may clip a large amount of one nail, rather than a small amount of each nail. The participant should not clip both his/her fingernails and toenails in order to get a total of 10 nails.

AASK Cohort Study



Instructions for Participants

It is very important that you use the nail clippers that we have provided because they have been specially designed to avoid contamination from the metal of the clipper. The nail clipper is yours to keep. Don't worry if you have clipped your fingernails within the last week or so – we only need thin slivers (approximately 1mm), so please give it a try. Please refer to the pictures on page 2 to help guide you through the process. If possible, please clip all 10 of your fingernails. If you are not able to clip every finger nail, please clip as many as you can. While clipping your fingernails, please place your hand over a flat surface and hold the nail clipper level to the surface.

We prefer that you clip your fingernails at the AASK clinical center. However, if you cannot provide fingernail clippings today, you may either clip your toenails instead, or you may clip your fingernails from home at a later date. Do not clip both fingernails and toenails, combining them in the same bag.

To clip your fingernails at the clinic today please follow these instructions:

1. To use the clipper, lift the large lever up. Underneath this will be a smaller lever; flip this over forming a closed compartment to capture the nail clippings. Then, flip the large lever back to its original position.
2. After clipping your fingernails, reverse the small lever and carefully empty the clippings from the compartment into the small, clear plastic bag that we have provided.
3. Please answer the questions on the form entitled “CBL Nail Clipping Mailing Form.”
4. Return the plastic bag containing the clippings and the data collection form to an AASK staff member. You may keep the nail clipper.

If you clip your nails after you leave the clinic:

1. Follow steps 1 – 3 above.
2. Place the plastic bag and the questionnaire inside the self-addressed stamped envelope that we have provided and place the envelope in the mail.

Thank You

Please provide 10 nail clippings that are at least 1 millimeter tall



Step 1



Step 2



Step 3



Step 5



Step 4

CHAPTER 20. STUDY COORDINATOR

20.1 Introduction

The AASK Cohort Coordinator plays an integral role at each Clinical Center of the AASK Cohort, working with the Principal Investigator and Co-Investigator, insuring that the entire study runs smoothly and the protocol is being implemented correctly to collect quality data. The Study Coordinator must promote a team approach and work closely with all staff, which may include the following:

Secretary and or Receptionist or staff whose responsibility it is to schedule participants to maintain adherence to follow up visits within the designated window.

The Study Coordinator must ensure that all staff taking blood pressures are accurately following the protocol and that the appropriate forms are being completed. It is also the coordinator's responsibility to make sure that all staff is up to date on certification.

For all personnel who are responsible for entering study data, the coordinator must see that the data entry is done in a timely and accurate fashion.

The AASK Cohort Coordinator is responsible for maintaining up-to-date certification for all personnel and maintenance calibration of sphygmomanometers.

All AASK Cohort Coordinators must participate in central training and recertification in order to be certified to participate in the AASK Cohort. This training assures that all Coordinators are properly trained and that data is collected in a uniform and standard fashion at all centers. At the training, Study Coordinators are trained and certified in several areas: forms completion, entering data in the oracle database, and responding to data discrepancy inquiries. Those who will be measuring blood pressures are also trained in measuring blood pressure using the Tycos Classic Hand Aneroid manometer and will be responsible for following and maintaining the AASK Cohort BP protocol. The Coordinator will work on counseling for adherence and for eliciting information from study participants in a uniform manner.

The Coordinator must be trained and ready to handle all aspects of the study in the absence of other personnel. If the Study Coordinator should leave the position before the completion of the study, he/she should train the replacement (if at all possible). Any new Study Coordinator must be certified by the Data Coordinating Center.

Each Study Coordinator must be thoroughly familiar with the Protocol and Manual of Operations and must keep copies current by inserting any revised pages, and is also responsible for maintaining copies of all study correspondence. The Coordinator is also responsible for making sure that all IRB communication and approval are achieved and that all correspondence is maintained. He or she will serve on the Study Coordinator's Subcommittee and will act as a liaison between the clinical center and the DCC, making

sure that needed information reached the appropriate persons. He/she will work with other Study Coordinators in the development of good study practices.

20.2 Participant Instructions During Consenting and Follow-up

Study Coordinators assume the primary role of assuring that participants are instructed in the goals and responsibilities of the AASK Cohort. This includes making sure that all participants have signed the informed consent at the appropriate time. In cases where the coordinator serves as the Blood Pressure Technician, he or she will do all of the instruction; however in cases where the Coordinator is not the Blood Pressure Technician, he/she will work closely with this person to ascertain that all procedures are carried out.

The Study Coordinator is responsible for making sure that an AASK Study Cohort file is established for every participant who enters the Cohort. This file includes all study forms for each participant and all other pertinent medical history information.

Following the signing of informed consent, the Study Coordinator will assure that participants are scheduled for all required procedures including: routine blood pressure monitoring, EKG, ECHO, 24 hour ambulatory blood pressure monitoring, fingernail collection, blood and urine laboratory studies and questionnaires. The DCC will provide a follow-up appointment schedule that will include the visit windows for each participant visit.

20.3 Monitoring and Promoting Adherence

The Study Coordinator must implement adherence promotion strategies utilized in the AASK Cohort. The Study Coordinator must try to maintain that all staff interactions with the study participants are consistent with maintaining a general environment intended to promote adherence. Each participant should be given an individualized plan for lifestyle modification at the appropriate protocol visits. Participants should also be given educational material if any lifestyle modification is required. Review of this material should be done by the Study Coordinator or if necessary by a dietitian or other staff.

20.4 Hospitalization and Death Procedures

Adverse events are defined as significant clinical events that are potentially related to the intervention or death.

The Study Coordinator is responsible for completing the Hospitalization Form for an adverse event requiring hospitalization. When a participant is hospitalized or experiences an adverse event, the Study Coordinator must notify the DCC in a timely fashion by the submission of the Hospitalization Form. If a participant refuses to be hospitalized, this should be noted in the clinic chart. The Coordinator may be asked to provide primary documents such as the hospital discharge summary to the DCC at the request of the Clinical Management Subcommittee.

All deaths will require the Study Coordinator and Study Physician to notify the DCC immediately via the Death Notification Form.

The Study Coordinator will also be responsible for sending the DCC any primary paper documents surrounding the death. These include death certificates, autopsy reports, and hospitalization discharge summary if death occurred in the hospital.

20.5 Dialysis/Transplantation

It is the Study Coordinator's responsibility to complete the appropriate forms in the event of the need for renal replacement therapy (RRT). In the event of RRT, the Coordinator must continue to schedule follow-up visits according to protocol. Outcome measures are documented in the same fashion.

20.6 Ordering and Filing Data Forms

The Study Coordinator is responsible for maintaining updated data collection forms to be used by the clinic.

20.7 Electronic Mail (E-Mail) Files

The Study Coordinator is primarily responsible for ensuring e-mail is printed and distributed as needed.

20.8 Logs or Minutes of Staff Meetings

The funded AASK Staff members at each clinic should meet regularly during the Study. Weekly meetings are recommended. The Study Coordinator should keep a log of when these meetings were held, who attended, and any major issues raised or resolved.

20.9 Study Site Visit

Site visits may be made to clinical centers. The Study Coordinator will play a key role in preparing staff for the site visits. The primary goals of the site visits are: to raise/improve communication between the study administrator, the clinic personnel and the DCC; to demonstrate the study's concern for quality of data collection; to discuss pressing current issues such as recruiting or adherence.

Site visit teams may consist of a DCC staff member familiar with the AASK Cohort protocol and blood pressure requirements and a NIH representative. A Study Coordinator from another clinical center may also be included.

Throughout the course of the study, each Clinical Center's performance will be monitored by a series of reports. These include reports of number of missing forms, rates of invalid data, rates of patients lost to follow-up, and number of missed visits. These reports will

routinely be sent to the Clinical Centers, the Steering Committee, and the NIH Program Office.

CHAPTER 21. GUIDELINES FOR USE OF BIOLOGICAL SPECIMENS IN THE AASK TRIAL AND AASK COHORT STUDIES

21.1. Overview

This policy covers all centrally stored biological specimens (urine, toenails and blood including DNA) that have been collected in the AASK trial and the AASK Cohort Study. The AASK Biological Specimens Allocation (ABSA) Committee consists of members from the AASK Publications and Ancillary Studies Committee, the NIDDK, the Data Coordinating Center (DCC) and the AASK Executive Committee. A catalog of all proposals/authors and reviewers will be the responsibility of the Data Coordinating Center. The ABSA Committee will review all requests for biological specimens **every three months**.

An active AASK investigator must be involved as an investigator on each project. The AASK investigator may be either an AASK principal Investigator or co-Investigator. If a non-AASK investigator submits a proposal, at least one AASK investigator must be added as an investigator on the proposal. If a non-AASK investigator submits a proposal from a non-AASK affiliated institution, they must find, with the help of the ABSA Committee, an AASK investigator willing to participate in the project. In the case where two very similar proposals are submitted with little distinction in scientific scope, the application submitted by an AASK investigator will be given priority.

The procedures for submitting a request for biological specimens, reviewing the proposals, and distributing the biological specimens are described below. Because the volume of biological specimens is limited, all meritorious requests cannot be approved.

21.2 Request for Use of Biological Specimens

The request for specimens **MUST** contain the following information:

1. Biosketches of the Principal investigator and other co-investigators (*must be in NIH format*)
2. Abstract
3. Hypothesis to be tested
4. Background and significance (maximum of *two* pages)
5. Design-Methods-Key References (maximum of *four* pages)
6. Description of specimen request (maximum of *two* pages)
 - a) **Specific type(s) of samples**
 - b) Volume of each sample
 - c) Time of sample collection (baseline vs. post-baseline) – Proposals that require baseline biological specimens (vs. post-baseline) must provide a strong rationale for use of the baseline specimens.
 - d) Use of thawed vs. unthawed specimens - for blood and urine, proposals must indicate whether previously thawed specimens can be used. The use of unthawed specimens will require a strong rationale.
 - e) Number of participants

- f) Type of storage – for urine, -20 or -70⁰F
 - g) Proposed laboratory that will perform the assays
 - h) DNA specimens – all proposals that require DNA must involve Dr. Lipkowitz at Mt. Sinai Medical Center in New York. His group has viable cell pellets and has a data bank of DNA.
7. Need for other study data (e.g. baseline and/or follow-up data) and other study resources.
 8. Time table with key dates (grant submission, target date for receipt of specimens, and completion of study)
 9. Documentation of local IRB approval [required prior to release of specimens]
 10. Agreement to return any unused biological specimens
 11. Budgetary issues
 - a) Source(s) of funding
 - b) Draft budget that includes costs of shipping, assays and other costs identified by the Data Coordinating Center (e.g., costs of preparing data request and aliquoting specimens). For all request, applicants are advised to contact Dr. Gerald Beck. For DNA requests, applicants should also contact Dr. Lipkowitz.

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21.3 The Review Process

Submitted proposals will be reviewed by the ABSA Committee. This committee contains at least one representative from each of the following: the NIDDK, the AASK Executive Committee, the AASK Publications and Ancillary Studies Committee, and the AASK Data Coordinating Center. The names of the members of this committee will be available. Applicants can also recommend ad hoc reviewers for their proposal; however, the final decision regarding the review rests with the ABSA Committee.

All members will be responsible for reviewing all protocols. Two members of the committee, a primary and secondary reviewer, will be appointed by Gerald Beck from the DCC with input from the Committee, to critique each protocol for scientific merit and feasibility. They will be expected to summarize their findings and make a recommendation that will be submitted to Gerald Beck for dissemination to the committee. The Chair of the Committee will review all proposals, and will review the evaluations, and discuss the status with the ABSA Committee before a vote is taken and a final recommendation made. These reviews need to be submitted within three weeks of receipt and before the next conference call that will discuss them. A quorum of the ABSA Committee, including all reviewers of a protocol to be discussed should be available for calls upon which a decision will be made.

The criteria for review of specimen requests for determination of acceptability and determination of conflict of interest will be similar to those used by NIH peer reviews. Projects will be reviewed according to:

1. Significance and Applicability

Does this study address an important issue relevant to progression of kidney disease or its complications in African-Americans? If the aims of the application are achieved, how will scientific knowledge be advanced?

2. Scientific Approach

Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation

Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

4. Investigator

Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers?

5. Environment

Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements?

6. Funding

Does this proposal have specific funding? Is the funding adequate to perform the work?

21.4 Release of Biological Specimens

Each group represented on the ABSA Committee will have a single vote. All decisions of the Committee will be determined by majority vote and the NIDDK Project Office will review all decisions by the Committee.

The Committee can approve a proposal for access to biological specimens, deny a proposal for access to biological specimens, or provisionally approve a proposal that is deemed likely meritorious but requires some additional changes before approval. A provisional approval will lapse six months after the initial Committee decision if no resubmission is made.

An investigator whose proposal fails to meet the criteria for access to biological specimens is entitled to constructive criticism about the proposal and resubmissions will be accepted. The decision of the Committee regarding access to biological specimens for a given proposal will be made available to the applicant within two weeks of the review. Proposals will be reviewed every three months.

Initial submissions to a funding agency that requires proof of access to AASK biological specimens will be considered and, if felt to be meritorious, a letter affirming the willingness of the AASK ABSA Biological Specimens Committee to provide biological specimens will be provided for the submission.

The type and quantity of biological specimens requested may affect whether the request can be filled and how quickly this can be done. An investigator whose proposal is approved for biological specimens cannot be guaranteed immediate access to biological specimens.

The proposals that have been approved for access to biological specimens will receive biological specimens as follows.

The list of investigators awaiting biological specimens will be stratified by type of specimen (blood, urine DNA, and toe nails). For each, the priority will be determined only by the date placed on the approved list. In other words, the most recent investigator approved will be at the bottom of the list (for whatever type of biological specimens he/she requires). Once an investigator receives biological specimens, requests for additional biological specimens must be preceded by providing the Committee an update of the research progress and IRB approval, and then his/her name will be placed at the bottom of the list. All investigators receiving biological specimens need to submit an annual progress report to the DCC. Publication of results needs to follow the AASK Publications Policy.

Investigators who feel unfairly treated either in terms of denial of a proposal for investigation or receipt of biological specimens may address complaints to the NIDDK Project Officer for AASK.

CHAPTER 22. CONSENT TEMPLATES

22.1 Consent Templates

Attached is a template of the “Consent Form” and the “Genetics Consent Form.”

23. PUBLICATION POLICY

23.1 Introduction

The policy of the AASK Study concerning publications and presentations is designed to achieve five objectives:

- i. To assure timely publication of the results of the AASK Study to the appropriate professional audiences,
- ii. To avoid premature publication of results that might compromise the performance of the study (such as by publication of trends of results before such trends become statistically convincing) or that might compromise the ability to publish the results in high quality peer reviewed journals (as by premature release to the lay press),
- iii. To maintain high standards of quality of all material published by the AASK Study,
- iv. To guard against duplicate publication of results by assuring absence of overlap of materials prepared by various writing committees, and
- v. To assure equitable attribution of credit to all of the professionals participating in the AASK Study.

To accomplish these ends, it is the policy of the AASK Study that preparation of all publications or presentations, other than materials prepared for local publicity purposes, must be assigned by the Study Chairman after consultation with Chairman of the Publications and Ancillary Studies (PAS) Subcommittee to specifically appointed writing committees, and that all such materials must be reviewed and approved by the PAS Subcommittee and/or the Steering and Planning (S&P) Committee before publication.

23.2 Scope of Policy, and Exception for Local Publicity Materials

All material to be presented orally or submitted for publication or dissemination by individuals associated with the AASK Study and dealing with any aspect of the AASK Study must receive prior review and approval by the PAS Subcommittee/S&P Committee with the following exception:

Material prepared for publicity purposes either nationally or within the recruitment region of an AASK Clinical Center, or presented orally or as handouts or posters to professional audiences solely for the purposes of informing the profession of the AASK Study and its objectives, need not be reviewed by the PAS Subcommittee. Such material must be limited to a background discussion of the issue of blood pressure control as a treatment for progressive renal disease and a description of the AASK Study organization, objectives, and entrance criteria, and to results of the study that have previously been presented to a scientific body or published in a scientific journal. It must not include discussion of any previously unrepresented and unpublished AASK Study outcomes or other citable professional reference.

23.3 Source of Suggestions for Publications of the AASK Study

Suggestions for topics appropriate for preparation of abstracts, peer reviewed papers or chapters and reviews are made by the PAS Subcommittee, in addition, all participants in the AASK Study are invited to suggest topics appropriate for preparation as abstracts, peer reviewed papers, or chapters and reviews from the AASK Study. Such suggestions should be made to the DCC and the Chair of the PAS Subcommittee, who shall review the request to be certain that there is no overlap with materials previously assigned to other writing committees. Where such overlap exists, the Chair of the PAS Subcommittee may make recommendations to the Study Chair that the suggestion be referred to an existing writing committee, that additional study participants be added to existing writing committees, or make other suggestions to resolve the overlap. However, final decision in this matter will be made by the Study Chair after consultation with the Chair of the PAS Subcommittee.

It is the policy of the AASK Study to encourage non-physician professionals to prepare scientific presentations to their own professional meetings and to prepare scientific papers for their own professional journals in addition to participating in the preparation of papers for medical journals. Since the subject matter of these reports and papers may well overlap with material being prepared by writing committees for medical journals, it is the policy of the AASK Study that under these circumstances, rather than forming a new writing committee, such non-physician professionals should be added to the existing writing committee concerned with related matters, specifically for the purposes of preparing such reports. The authors of these presentations and reports will be the members of the writing committee, with first author being the individual added to the committee for this purpose, using the appropriate authorship style described in section 1.6.

In addition, the PAS Subcommittee will formulate and maintain a list of suggested topics that should be prepared for publication, to assure that all completed aspects of the work of the AASK Study are reported to the scientific community in a timely fashion.

23.4 Assignment of Writing Committees

Topics suggested for presentation or publication that do not overlap with an existing committee will be circulated to the Principal Investigators of all clinical centers, DCC, central laboratories and the NIH. These groups are requested to suggest and justify names for lead authors (Chair of writing committees) and co-authors. These names will be collated and reviewed by the PAS Subcommittee. A recommendation for a writing committee will then be made to the Study Chair who will decide on the final composition of the writing committee after consultation with the Chair of the PAS Subcommittee. If a topic is suggested by a participant of the AASK Study, the writing committee will be formed as just described except that the person making the suggestion will be considered as the potential lead author. The Principal Investigator of an ancillary study should be considered for lead author of material derived from this study. If only a subset of clinical centers participate in an ancillary study, only investigators from these centers should be considered to be on writing committees relating to this study. Appointments of writing committee chairmanships will be made in an equitable fashion to all professionals -- physicians, study coordinators,

nurses, statisticians, and others -- in a fashion that recognizes the special contributions of each member of the AASK Study to its performance. Any dispute about lead author or co-author will be settled by the Study Chair after consultation with the Chair of the PAS Subcommittee. In all cases, writing committees dealing with an issue that requires analysis of data by the Data Coordinating Center will have a member of the DCC assigned to it.

From time to time it may be expedient for the chairmanship of a writing committee to be reassigned to another member of that committee, or for members to be dropped from or added to a writing committee. The Chair of the PAS Subcommittee and Study Chair are authorized to make such changes with the consensus of the members of the writing committee, or on their own authority where there is clear cause.

23.5 Reports of the AASK Study: Classes of Reports

There are four classes of reports of the AASK Study:

- A. Reports of the major outcomes of the Study. It is assumed that there will generally be only one or two such reports derived from each Phase of the Study.
- B. Reports addressing in detail one aspect of the AASK Study, but in which the data are derived from the entire study.
- C. Reports of data derived from a subset of centers by members of the AASK Study, (e.g., substudies or ancillary studies), or originally conceived analyses of data from the entire AASK Study (original analyses).
- D. Reports of investigations initiated outside of the AASK Study, but using data or samples collected by the AASK Study. The investigators may be AASK or other investigators, but the source of the ideas and the funding for the study will have been derived outside of the AASK Study itself. Writing committees for this type are formed and presentations and publications made in accordance with the general policy rules for AASK publications. However, the Principal Investigator of an ancillary study should take primary responsibility in publishing the results of the study.

23.6 Authorship Policy

The authorship policy of the AASK Study must achieve two somewhat conflicting goals. First, it is recognized that the findings of the study, especially the findings reported in Type A and B reports, are derived from the efforts of the entire AASK professional staff. Thus, all reports, of whatever Type, must give recognition to all the participants of the AASK Study, and reports of Types A and B must give primary recognition to the entire study professional staff. On the other hand, it is recognized that the preparation of a manuscript places special demands on the assigned writing committee, and especially on the Chair of the writing committee. Further, recognition of special effort and achievement is important in the professional careers of the study staff, and specific listing as an author is a significant motivating factor that will help assure prompt completion of writing assignments and timely publication of the results of the AASK Study. The AASK authorship policy attempts to recognize each of these goals. The authors of AASK publications will be listed as detailed below for each type of publication.

Type A publications:

abstracts: from the African American Studies of Kidney Disease¹, presented by XXXX.

papers: from the African American Studies of Kidney Disease¹, prepared by XXXX.

¹The AASK participant box, detailed below, must be included in these papers. If a journal's publication policy does not allow authorship by a group, the authors will be listed first as in Type B publications.

Type B publications:

abstracts and papers: Authors' names, from the African American Studies of Kidney Disease¹

¹The AASK participant box will be included in all papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A papers. It will not be practical to publish the entire list of participants in abstracts.

Type C and Type D publications:

abstracts and papers: authors' names and the AASK Study

¹The participant box will be included in all Type C papers if this can be arranged with the publisher. Otherwise it will be referenced in one of the Type A papers. In Type D papers, the list of participants will be referenced in all cases. It will not be practical to publish the entire list of participants in abstracts.

23.7. Authorship: Professional Participants Listing in the AASK Participant Box

The AASK participant box will list all professionals that have participated in the AASK Study for a minimum of one year. The participants for each participating center will be listed together, with the center Principal Investigator listed first, and identified as "P.I." followed by the other center staff listed alphabetically. Each participant will be listed only by his/her professional and academic degrees, not by the specific position that she/he held in the study. The centers will be listed in the following order:

NIH

Study Chair

Clinical Centers (in alphabetical order)

DCC

Central Laboratories (in alphabetical order)

Prior to the publication of any papers from the AASK Study, each center will be asked to confirm and approve the listing of the personnel from that center in the AASK Participant Box.

23.8 Acknowledgement of Support and Reprint Addresses

Acknowledgement of grant support to be used in all papers reporting results of the AASK Study. (In the case of ancillary studies, additional sources of support should be cited as appropriate).

The AASK Study is supported by the Division of Kidney, Urologic and Hematologic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, NIH. Additional support is provided by the (list of any industrial or other support).

The following information regarding reprint requests should be included in all papers prepared for the AASK Study. The DCC will maintain an inventory of all AASK Study publications and will mail out the reprints.

Requests for reprints should be addressed to:
AASK Data Coordinating Center
Department of Biostatistics and Epidemiology, Desk P88
The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio 44195

23.9 Schedule for Completion of Writing Assignments and Resolution of Overlaps Between Writing Committees

At the time that a writing committee is constituted, the PAS Subcommittee will establish a timetable for the completion of the writing assignment that takes into account deadlines for the publication, the amount of time that will be required for data analysis, the other commitments of the DCC, and the priority of the publication. The Chair of the Writing Committee should provide the Chair of the PAS Subcommittee a general outline of the proposed publication within a month of receiving its assignment, to permit the PAS Subcommittee to identify any overlap with the assignments of other writing committees, and to permit establishment of an appropriate timetable. Where overlaps of materials to be covered by different writing committees are detected, the Chair of the PAS Subcommittee will attempt to resolve these informally with the chairs of the involved writing committees. In the event that this effort at mediation fails, the issue will be resolved by the Study Chair. The Chair of the PAS Subcommittee will report at each meeting of the S&P Committee on the progress of the various writing committees.

23.10 Review of Abstracts and Presentations by the PAS Subcommittee

To expedite review of abstracts, oral presentations, and any other material for which there is an explicit deadline for submission, the following procedure will be used:

- i. The writing committee wanting to submit an abstract, give a talk, or submit

other material for which there is an explicit submission deadline shall contact the Chair of the PAS Subcommittee. In the event that the Chair is unavailable, the Alternate Chair may be contacted. The Chair (or Alternate Chair) will name a subcommittee of three members of the PAS Subcommittee to review the submitted material and will inform the submitter and this subcommittee of their appointment. The submitted material should be mailed by the submitter directly to these three reviewers so as to reach them no fewer than seven (7) days prior to the deadline for submission.

- ii. The members of the subcommittee shall review the material and notify the Chair solely of their approval or disapproval. If there is unanimous approval, the PAS Subcommittee Chair (or Alternate Chair) shall inform the submitter that he/she has AASK Study approval for the submission. In the event of a split vote for approval, the issue will be reviewed by the PAS Subcommittee Chair (or Alternate Chair) with the Chair of the AASK Steering & Planning (S&P) Committee (or in his unavailability with the Vice-Chair of the S&P Committee) whose decision will be binding.
- iii. All materials submitted for approval in this fashion will be distributed by mail, together with notice of the disposition, to all members of the PAS Subcommittee and to the Chair of the S&P Committee. All approved materials will also be forwarded to the NIH Project Coordinator, and for record purposes to the Principal Investigator of the Data Coordinating Center, and will be distributed to the entire membership of the S&P Committee at the next meeting of that Committee.

Approval for submission of an abstract or oral presentation does not automatically grant approval of the material ultimately to be presented. This material must also be submitted for review and approval in accordance with the above rules at least seven (7) days prior to the scheduled oral or poster presentation. Normally this review will be done by the same subcommittee of the P&As Committee that reviewed the initial abstract.

- i. In the case of an oral presentation, an outline of the talk and a copy of any slides to be used must be submitted for review.
- ii. In case of a poster presentation, the content of the poster material must be submitted for review.

23.11 Review of Papers by the PAS Subcommittee

All materials for which there is no explicit deadline, and all full papers that may result in a citable scientific reference, whether or not there is a deadline for submission, must be submitted to the Chair of the PAS Subcommittee for formal review by the entire Committee. If there is a deadline for submission of a formal paper, it is the responsibility of the submitter to be certain that it is submitted to the Chair, PAS Subcommittee, at least 30 days prior to the deadline, to permit such review. This review will be conducted as follows:

- i. The Chair, PAS Subcommittee, shall appoint a panel of three primary reviewers, two of whom must be PAS Subcommittee members, and one of whom may be any professional member of the AASK Study Group with appropriate expertise. The Chair shall distribute the material to all members of the PAS Subcommittee and to the Principal Investigator of each center participating in the AASK Study. The three members of the review panel shall each prepare and send to the Chair a written critique of the submitted material for distribution to the entire PAS Subcommittee. The P.I.s of the various clinical centers will be given a deadline by which any comments or critiques that study personnel at their center may wish to make must be received by the Chair, PAS Subcommittee. This mechanism will assure that each professional participating in the AASK Study will have an opportunity to review any materials that will be submitted for publication bearing his/her name as a participant and co-author.
- ii. The Chair, PAS Subcommittee shall schedule a meeting of the Committee (generally by conference call), including review of papers and other non-time critical materials as Agenda items. The reviews of the panel members and any comments received from the center P.I.s will be distributed to the committee with the agenda.
- iii. While discussion of the submitted papers and other materials will be led by the three appointed reviewers, all members of the Committee will be invited to participate and all shall vote on final disposition.
- iv. In keeping with medical editorial traditions, there are three possible dispositions: approval of the material as submitted (possibly with some recommendations for revision that do not require re-review), non-acceptance of the material as submitted but with recommendations to the authors for revisions and resubmission, and disapproval of the material.
- v. The Chair, PAS Subcommittee shall be responsible for communicating the decision of the Committee to the authors, together with a summary of suggestions for revision, if any. If the Committee has recommended non-acceptance of the material as submitted but with suggestions for revision and resubmission, he and the writing committee may agree not to proceed with a report to the Executive or S&P Committees at that time, pending revision and resubmission.
- vi. If there is a recommendation for approval or final approval or final disapproval of submitted material, or if there is a recommendation for revision which is contested by the author(s), the Chair, PAS Subcommittee shall report this outcome in writing to the Executive Committee for final action. In the case of a dispute between the PAS Subcommittee and the author(s), the Chair, PAS Subcommittee shall provide a copy of the submitted material and a summary critique to Executive Committee, and the chair of the writing committee shall be given an opportunity to submit a rebuttal.
- vii. The authority to grant final approval for a formal scientific paper of the AASK Study rests with the S&P Committee, or the Executive Committee in the interim between meetings of the S&P Committee.

- viii. All materials submitted for approval in this fashion will be forwarded, together with notice of disposition, to the Chair of the S&P Committee. All materials receiving final approval by the Executive or S&P Committee will also be forwarded to the NIH Project Coordinator, and for record purposes to the Principal Investigator of the DCC.
- ix. In the event that editors of a scientific journal to which an approved AASK scientific manuscript is submitted suggest or require revisions of the manuscript, the revised manuscript must be reviewed again by the PAS Subcommittee prior to resubmission in the same manner as described above. Generally, the Chair will appoint the same reviewers that first read the paper to review the revision, and every effort will be made to expedite such repeat reviews.

23.12 Criteria for Review of Materials by the PAS Subcommittee

All materials submitted to the PAS Subcommittee will be reviewed for acceptability on two grounds:

- i. Materials shall be evaluated for scientific accuracy, quality, importance, and style. The intent is to assure that all approved AASK materials reflect well on the AASK Study.
- ii. Materials shall be reviewed to assure appropriateness of the content. The material shall be reviewed to assure that it conforms to the assignment to the writing committee, addressing satisfactorily the assigned topics and not encroaching on material assigned to other writing groups. In addition, the material shall be reviewed to assure that it does not divulge prematurely the outcomes or findings of the AASK Study or compromise the eventual publication of AASK findings in high quality peer reviewed journals. In this later regard, it must be remembered that publication of reports of more than 400 words are generally taken to constitute prior publication of a body of material and will generally preclude subsequent publication of the material in a peer reviewed journal.

23.13 Maintenance of Records of Publications and Presentations

The DCC will maintain a record of all official publications and presentations of the AASK, separated into the following categories:

- i. Peer reviewed papers accepted and published in professional journals
- ii. Invited editorials, reviews, chapters, and books
- iii. Abstracts published in citable journals
- iv. Other presentations at regional or national meetings which do not result in a citable abstract.

This listing will be updated at least every six months and will be distributed to the P.I. of each center participating in the AASK Study, together with reprints or copies of any papers, chapters, or abstracts accepted for publication since the last update. This is intended to facilitate the updating of curricula vitae and the timely submission of reports to CRCs and other such organizations within the participating centers.

23.14 Acknowledgement and Acceptance of AASK Policies on Publications and Presentations by the Professional Participants in the AASK Study

To assure that all professionals involved with the AASK Study know and understand the policies of the AASK Study, and to preclude the possibilities of misunderstandings after initiation of the Study, each professional member will be given a copy of this Chapter and will be asked to sign a Statement of Understanding Form (see next pages) listing the major provisions of the Chapter and attesting to his/her acceptance of these policies. The original of the signed Statement of Understanding Form should be returned to the DCC for record purposes. The copies of the Chapter and the signed Statement of Understanding Form should be kept by the AASK professional participant for reference.

CHAPTER 24. AASK ANCILLARY STUDIES POLICY

24.1 General Policy

To enhance the scientific output of the AASK Study, including both the trial and cohort phases, the AASK Steering Committee welcomes proposals from individual investigators to carry out ancillary studies. Nevertheless, to protect the integrity of the AASK Study, ancillary studies must be reviewed and approved by the relevant AASK Committee(s) as outlined below.

24.2 Definition of an Ancillary Study

An ancillary study is one based on information from AASK Study participants in an investigation or analysis which is relevant to, yet not described in the AASK Study protocol. It is anticipated that a typical ancillary study will require additional data not collected as part of the routine AASK Study data set. Ancillary studies may be submitted by the investigators within the AASK Study or by investigators without a prior relationship to the AASK Study. Ancillary studies often require external (non-AASK Study) funding. Examples of funding sources include grants funded by investigator-initiated NIH research awards (RO1s) and grants from academic institutions or private sources (e.g. private foundations, pharmaceutical companies). Any ancillary study must have sufficient funding to cover the costs incurred by the AASK Clinical Centers and Laboratories (e.g., to process or ship samples) and by the Data Coordinating Center (DCC) for tasks such as selecting samples, preparing and documenting analysis files, conducting and interpreting statistical analyses, and integrating the new ancillary data back into the combined AASK Study database. There are no funds available for these purposes within the AASK Study.

24.3 Requirements and Procedures for Approval of an Ancillary Study

24.3.1 Overview

Initial review and concept approval is required by the AASK Publications and Ancillary Studies (PASC). The PASC Chair or designee will assign primary and secondary PASC reviewers. Potential outcomes are approval, conditional approval, and disapproval. Once approved by the PASC, the AASK Cohort Chairs Committee, acting on behalf of the AASK Steering Committee, must also provide concept approval. Under specific, selected conditions (e.g. an imminent funding deadline), the AASK Cohort Chairs Committee or its Chair may provide conditional approval pending review by the PASC. Any issues of concern to dissenting voters will be shared with the applicant and opportunities for clarification provided.

Additional approval from the clinical centers may also be required. Any ancillary study requiring the conduct of new procedures or the collection of sensitive information will require approval by the PI of each participating center and presumably its IRB. However, if the new data are merely questionnaire responses from a brief instrument or

analyses of stored specimens, approval from the PI of each participating clinical center will not be required. Investigators are encouraged to discuss potential proposals with the Chair of the PASC, Coordinating Center statistician or investigator, or the Chair of the AASK Study.

All ancillary study proposals must include at least one AASK investigator as a co-investigator. Willingness to include additional AASK investigators as co-investigators of the ancillary study is mandatory.

24.3.2 Requests for Ancillary Studies as Part of Training or Career Awards

The AASK Study investigators and the NIH anticipate that the AASK Study will be an important resource for career development and training among members of the academic community. Special consideration, therefore, will need to be given to requests for ancillary studies to be funded through training grants or career development awards through the NIH or other funding sources. As these funding mechanisms typically provide funding only for investigator effort, not additional data collection, such proposals will generally propose research questions and analyses that could be considered part of the core AASK Study. Evaluation should consider the scientific gain to the AASK study from the addition of the proposed ancillary analyses as well as the training and career development opportunities afforded to the applicant by the proposed ancillary study.

24.3.3 Considerations for Approval

- A. The proposed study must be scientifically meritorious, based on meeting the traditional requirements of scientific review (i.e. significance and applicability, scientific approach, innovation, investigator, environment and funding).
- B. Participant burden
 1. The proposed study must be acceptable to the participants (e.g. time, discomfort, privacy).
 2. The proposed study must not interfere with other parts of the main AASK Study.
 3. The proposed study must not hamper continued participation in the main Study.
 4. The proposed study must put minimal demand on scarce AASK Study resources such as blood samples.
- C. The proposed study must require the unique characteristics of the AASK Study cohort to accomplish its goals.
- D. The investigators must have adequate resources to effectively complete the project, including:
 1. Sufficient budget and personnel
 2. Staff having the requisite expertise to meet the objectives of the project.
- E. The ancillary study investigators must agree to return the complete ancillary data set back to the AASK Study.
- F. The proposed study must not adversely divert study resources (personnel, equipment or study samples) or investigator/staff time.
- G. The proposed study must not jeopardize the public image of the AASK Study.

- H. The investigator must indicate a willingness to follow AASK study guidelines, particularly a willingness to include other AASK investigators as part of the research team and to follow AASK procedures, including its publication policy.
- I. The proposed ancillary study must not overlap with other ancillary studies or other anticipated AASK analyses.

24.3.4 Instructions for Preparation of Requests for Approval of an Ancillary Study

All proposed ancillary studies must be submitted to the DCC in time for circulation and subsequent review by PASC and then the AASK Cohort Chairs Committee or its Chair before submission to a funding agency. Studies submitted for review less than 8 weeks before a funding application deadline may not receive approval. Under specific conditions (e.g. an imminent funding deadline), the AASK Cohort Chairs Committee may provide conditional approval, contingent upon subsequent PASC review. The following are the elements to be included in an ancillary study proposal.

24.3.5 Proposal Format

A written request for approval of an ancillary study should be submitted to the PASC as a brief, typically three to four page, concept document containing the following information:

- A. Identifiers:
 - 1. Initiating investigators, collaborators, AASK Study co-investigator. A biosketch of non-AASK investigators is also required.
 - 2. Planned starting date and project timeline
 - 3. Funding plans and estimated cost
- B. Design and Methods
 - 1. Brief background and rationale
 - 2. Study questions or hypotheses
 - 3. Specific data collection methodology, including questionnaires and coding forms, if available.
- C. Specific answers to the following questions
 - 1. What is the expected burden to participants? What are the time burdens, discomfort and expected participation rates?
 - 2. What AASK Study core data and/or analyses are needed for the ancillary study?
 - 3. Are biological samples (blood, urine, or finger nails) required? If yes, the following questions must be answered or addressed:
 - a) Specific type(s) of samples
 - b) Volume of each sample
 - c) Time of sample collection (baseline vs. post-baseline) – Proposals that require baseline biological specimens (vs. post-baseline) must provide a strong rationale for use of the baseline specimens.
 - d) Use of thawed vs. unthawed specimens - for blood and urine, proposals must indicate whether previously thawed specimens can be used. The use of unthawed specimens must be justified.

- e) Type of storage – for urine, -20 or -70C
 - f) Proposed laboratory that will perform the assays
 - g) DNA specimens – all proposals that require DNA must involve Dr. Lipkowitz at Mt. Sinai Medical Center in New York. His group has immortalized cells and has a data bank of DNA.
4. What collaboration with AASK Study investigators is planned? With whom? Have the collaborating investigators approved the proposal?
 5. What, if any, follow-up is needed? Specify length of time and events to be ascertained.
 6. What sample size is required? Ancillary studies must document adequate statistical power, especially for studies that require new procedures or biological specimens.
 7. When will data be collected? Could the ancillary study be deferred to a later exam cycle?
 8. How will the ancillary study be funded? Would any additional un-reimbursed work or personnel time be expected of the AASK Study? How will the ancillary study budget cover demands on AASK Study personnel time and Study resources?
 9. Where will the data analyses be conducted? Under most circumstances, the Data Coordinating Center will perform the analyses.
 10. How will the confidentiality and other aspects of protection of human subjects be maintained?
 11. When and in what form will a complete data set be returned to the AASK Study?
- D. Data or Specimen Requirements:
1. Data needed from AASK Study analysis files
 2. Specimens needed from AASK Study repositories, specifying type and amount
- E. Handling of AASK Study Data and Specimens:
1. Disposition of stored samples from main study and those processed by ancillary study
 2. Disposition of ancillary study data at the conclusion of the ancillary study

24.4 Changes to Proposed Study

Once an ancillary study is approved, if a substantive change occurs in the design or if new data collection elements are added, such changes should be disclosed to the PASC, for review and approval.

24.5 Proposal Budget

The investigator applying for an ancillary study must supply all additional funds needed to successfully complete the study. The PASC will be concerned with both the obvious and the hidden costs to the AASK Study entailed by an ancillary study. Such costs include, but are not limited to:

- a) Statistical and data management staff for coordinating data management and analyses.

- b) AASK Study expenses involved in altering key identifying data so that subjects' confidentiality will be protected.
- c) Costs for notification of alert values.
- d) If work is to occur on site, rental of appropriate clinic, lab and office space
- e) Personnel costs for arranging or conducting additional study visits, if required.
- f) Personnel, equipment and supplies necessary to complete the project.

Once a study concept is approved, applicants for ancillary studies must work in conjunction with the DCC to formally develop a budget that adequately provides for these types of expenses at both the DCC and Clinical Centers.

24.6 Human Subjects/Data Confidentiality/Monitoring

Confidentiality of AASK participants must be guaranteed. Individually identifiable data may not be released. A signed consent must be obtained from every participant in the ancillary study, if the data collection/request is not covered in the original informed consent process for the main AASK Study.

- a) Any investigator or personnel having access to AASK subject data must be certified in the NIH OHSR or equivalent training course.
- b) A copy of the IRB approval letter from the principal investigator of the ancillary study is to be sent to the DCC. If a separate consent form is required for the ancillary study, a copy of the signed ancillary study consent form for each study participant must be included in the participant's file.

The principal investigator of an ancillary study is responsible for presenting the study to the PASC as appropriate, and monitoring progress of the ancillary study. The AASK Steering Committee monitors the development of the ancillary studies, receipt of funding, initiation dates, and progress. The principal investigator of the ancillary study must submit a written progress report on ancillary studies periodically to the Steering Committee.

24.7 Analysis and Publication of Results of Ancillary Studies

Unless specifically arranged, all analyses will take place at the DCC and be conducted under the supervision of its biostatistician-investigators. Under specifically approved circumstances, datasets will be released for analysis by external investigators. Ancillary studies funded as career or training awards as well as studies taking place in a subset of clinical centers may be situations in which release of data for analysis deserves special consideration. Under these circumstances, the investigator of the ancillary study will provide interim reports on analyses to the DCC during data analysis to ensure that all study data used in analysis of ancillary study results are consistent with data in the main study database and to ensure the quality of analytical approaches.

Proposals for manuscripts resulting from ancillary studies shall be submitted for review to the PASC and require approval before establishment of a writing committee.

Abstracts and manuscripts from ancillary studies will also require PASC approval. Each manuscript and abstract would be expected to include a AASK investigator. The phrase "AASK Study" should be included in the title in all scientific presentations and manuscripts and listed as a key word whenever possible. Published papers should indicate that the research was conducted as an ancillary study to the AASK study. For papers publishing analyses not performed by the DCC, the publication should include a statement indicating that the investigators, not the DCC, performed the analyses.

Manuscripts should also acknowledge the contributions of the study participants and, if appropriate, list the AASK investigators and centers.

24.8 Feedback of Results of Ancillary Studies to Participants

Results of ancillary studies shall be reported to participants and/or their physicians if medically useful.

24.9 Handling of AASK Data and Specimens

At the time of distribution of AASK specimens and/or information, the AASK Collaborating Investigator, with help from the DCC, will make explicit arrangements with the ancillary study PI for the security of these study materials, and for their final disposition at the conclusion of the ancillary study. The safety and confidentiality of the AASK data at the collaborating institution is the responsibility of the ancillary study PI, as is the appropriate disposition of these materials after the study has been completed. Leftover DNA and laboratory specimens are destroyed or returned, and files of AASK data are returned or deleted, as established at the outset of the collaboration. An archival copy of the newly collected data and/or laboratory results not already held at the DCC will be sent to the AASK Coordinating Center at the conclusion of the data analysis and publication of the main (ancillary) study hypothesis. This transfer is the responsibility of the ancillary study AASK collaborator(s). Once transferred back to the AASK, these ancillary data will become part of the aggregate AASK data.

CHAPTER 25. PLAN – ALIQUOTING STORED SPECIMENS FROM THE AASK TRIAL

25.1 Background

- at the clinical centers, specimens were not processed, stored and shipped to ensure sustained storage at -70
- serum specimens were obtained in a fasting state
- at each time point, 2 aliquots of 1.8 ml serum were obtained
- at each time point, 2 aliquots of 3.6 ml urine from 24 hr urines were obtained
- only those assays of stable analytes should be performed

Based on a conference call held on May 19, 2004, the following was proposed and subsequently agreed upon by the Executive Committee:

25.2 Aliquoting Stored Specimens from the AASK Trial

1. serum (at the time first assay is performed)
 - a) one of the 1.8 ml serum is kept frozen
 - b) if assay to be performed by Dr. Van Lente's lab
 - i) Dr. Van Lente performs assay (e.g. for Coresh-Levey ancillary study: CRP, cystatin and possibly ANP, BNP assays on baseline and 24 m follow-up specimens- total volume required about .2 to .3 ml)
 - ii) aliquots remainder as follows:
0.5 ml, then .2 ml for as many aliquots as possible (this should result in one 0.5 ml aliquot and about five 0.2 ml aliquots)
 - c) if assay to be performed by lab other than Dr. Van Lente
 - i) Dr. Van Lente aliquots specimens as follows:
volume required for assay, then 0.5 ml, then 0.2 ml for as many aliquots as possible (this should result in one 0.5 ml aliquot and about seven 0.2 ml aliquots)
2. urine (at the time the first assay is to be performed)
 - a) one of the 3.6 ml urine is kept frozen
 - b) the other 3.6 ml specimen is divided as follows: the volume required for the assay, then the remainder into seven aliquots of 0.5 ml
3. Dr. Van Lente's lab to investigate use of bar code system to label aliquots
4. DCC to ask NIDDK to use carry over funds for aliquoting, estimated at \$7 per stored specimen, not including software.
5. Leftover specimen after assays – investigators will be asked to minimize thaw time and to refreeze leftover specimens as soon as possible. These will be shipped to the NIDDK repository, not discarded.

CHAPTER 26. CLOSE OUT

26.1 Close Out

Participant Close Out Visits should be held some time between March 1, 2007 and June 30, 2007. All participants should be seen during this time frame. Every effort should be made to locate any lost participants. Any missed ABPMs, ECGs or Echoes should be done at this time as well.

The following documentation was sent to the clinical centers prior to the start of Close Out.

AASK Logo stationery

Date

Name of study participant

Address

Dear Mr./Ms. _____

We want to take this opportunity to thank you again for your participation in the AASK Cohort Study. As you know, your participation in the AASK Cohort Study has produced much needed information that is of great importance to African American/Black patients with high blood pressure and kidney disease.

This is a reminder that **your next visit is one of the most important visits in the study**. As **one** of the **last** visits of the study, the information gained **from this visit will allow the best comparison** with the information obtained from **your earliest visits**.

We hope that you will continue to support the study with your participation. We have scheduled your appointment for _____.

In order to make the best use of your time during this visit, we have attached some reminders about your upcoming visit.

The AASK study is not over yet! It has been our pleasure following you throughout the study and we look forward to seeing you at this next visit.

If you have any questions, please feel free to contact us by phone at (local AASK clinic telephone number)

Thank you again for your continued participation in AASK.

Sincerely,

AASK Cohort Study Team

Strategies for Locating Participants Who Are Lost to Follow-up

Revised 05/16/2006

- 1) Identify one or more clinic staff who will be responsible to conduct search (retention, outcomes, other). This may vary across clinics.
- 2) Set up a process at your clinic to identify which participants are “lost to follow-up”, at the present time (beginning with “Summary of Inactive Participants Report”), and a process to identify participants, over time, as they become “lost”.
- 3) Suggestions for locating participants who are lost to follow-up.
 - a) Gather information from all clinic staff that may have information on the participant (clinic notes, phone calls, etc).
 - b) Tips for locating participants
 - i) Each case is different and may require different actions
 - ii) Look for clues in recent hospital records (e.g., was participant discharged to a nursing home or other medical facility?)
 - (1) Online resources for locating medical facilities
 - (a) The American Hospital Directory - www.ahd.com/
 - (b) Medical facilities in the US and abroad - <http://www.hospitalsoup.com/hospitalsearch.asp>
 - iii) Contact proxy (requires having proxy information on file or locating proxy)
 - iv) Send mail requesting forwarding address
 - v) Contact physician’s office
 - vi) Check real estate (i.e., has ownership changed?). Some states will list current address if ownership has not changed.
 - vii) Check public records
 - viii) Has there been a name change (e.g., was participant planning to marry or divorce)?
 - ix) Keep track of all steps taken to locate the participant and record what happened (including names of people with whom you have spoken).
 - c) Excel Business Solutions Location Services for Locating “Missing” Study Participants
 - i) Limited Address Location Search –Phase I \$10.00 per name submitted. Involves an effort to identify current addresses, telephone numbers, and vital status for study participants who became lost to follow-up. 1800 482-0940 or Sales@ExcelBusSol.com
 - ii) Extended Address location Search –Phase – 2 \$49.00 per hour (usually one hour is sufficient) This is used to typically locate a percentage hard to find participants who were not located in the Phase 1 search. This search involves an intensive search of multiple nationwide databases in an attempt to develop a listing of recently reported addresses, telephone info and death information if applicable. 1800 482-0940 or email: Sales@ExcelBusSol.com
 - d) Resources on the World Wide Web:
 - i) www.ancestry.com/
 - (1) This is a search by name and provides general information for a fee. See website for details.
 - (2) Annual membership is \$179.40, billed in monthly payments of \$14.95, as of 12/30/2005

- (3) Monthly membership is \$23.95 per month, billed in monthly payments, as of 12/30/2005
- (4) Be sure to read the “Terms and Conditions”
- ii) www.peoplefind.com
 - (1) This search does have a fee. You can also call 1888 563-Find. You can also call 1800 US Search
- iii) www.patientfind.com or call 248 399- 8234.
 - This company has been extremely successful in finding people with a 90% success rate.
- iv) www.ancestry.com/search/rectype/vital/ssdi/main.htm
 - (1) This is a Social Security Death Index (SSDI) search tool and is part of ancestry.com listed above. It is purportedly the most up to date and powerful SSDI available on the internet.
 - (2) Search will provide minimal information free of charge, but you will need further information to verify that the information provided is for the correct person.
 - (3) Index is purportedly updated monthly (other SSDI are updated less frequently).
 - (4) Paid membership information is as indicated above for ancestry.com.
- v) http://ssdi.genealogy.rootsweb.com/cgi-bin/ssdi.cgi?o_xid=0031936443&o_lid=0031936443&o_xt=31936443
 - (1) This is another SSDI search option and will provide DOB, date of death, last residence, and social security number for decedent free of charge.
 - (2) Index purportedly updated semi-annually.
- vi) http://www.ancestorhunt.com/prison_search.htm
 - (1) This is a prison inmate search. Scroll down to select state and begin search. Search will provide DOB, picture, location, sentence, etc. free of charge for some states. Other states may provide instructions for verifying that a person is incarcerated.
- vii) <http://www.ancestorhunt.com/county-jail-inmates-search.htm#County%20Jail%20Inmates%20Search%20by%20State>
 - (1) This is a county jail inmate search and is not provided by all counties.
 - (2) You may also call the county jail of interest and inquire by telephone.
- viii) <http://www.clearhq.org/boards.htm>
 - (1) This is a licensure, enforcement, and regulation search. If the participant’s profession requires a professional license or certification regulated by the state, you can check the status for most states. This information is free of charge.
 - (2) The search requirements vary according to state and profession, so read instructions carefully.
- ix) <http://www.whitepages.com/>
 - (1) E-White pages is a good tool for locating contact information for participants, proxies, and other contacts
 - (2) Free information
- x) <http://www.yellow.com/>
 - (1) E-Yellow pages is a good tool for locating physicians or other professionals/business owners.
 - (2) Free information
- xi) <http://www.zabasearch.com/>

- (1) Name search provides name, address, and date of birth free of charge
- (2) Search by telephone number requires payment of a fee.
 - (a) Instant report, \$14.95 (as of 01/05/2006)
- (3) Search by social security number requires payment of a fee.
 - (a) Background report, \$49.95 (as of 01/05/2006)
- xii) <http://www.google.com/>
 - (1) A tool to locate people and medical facilities.
 - (2) Free information
- xiii) Websites specifically for your city, county, or state.
 - (a) Check local medical center websites for physician directories.
 - (b) Check local newspaper websites for obituary information. Information, search options, and length of time available will vary by website.
 - (c) Check county website for real estate or geographic information system. This will allow you to search the database by property address.
- 4) If participants have requested no further contact from the study then check their status (dead or alive) every six months using alternative methods.
 - a) Social security death index (2 web options are listed above)
 - b) Real estate listings
 - c) Obituaries
 - i) If possible, check the local obituaries every morning to determine whether or not participants are listed. (Note: Obituaries usually list next of kin which might be helpful.)

Reports and Graphs that will be included in the “Post Close Out” E-Mail for AASK Participants

When the clinical center enters Form 111, 110, 140 and the CBL has entered the serum and urine results (Forms 124 and 125) for the Close Out Visit, the following reports will be generated overnight and will be sent to the clinical center via e-mail. It is the clinical center’s responsibility to photocopy these reports and review these with the participant. The clinical center should also send a copy of these reports to the participant’s Personal Care Physician.

**Normal values should be added to the tables

Serum: BUN (Kidney)
(fasting 10 hrs) Serum Creatinine (Kidney)
 Calcium
 Phosphorus
 Sodium
 Potassium
 Chloride
 Bicarbonate
 *Total Cholesterol
 *HDL (Good Cholesterol)
 *LDL (Bad Cholesterol)
 *Triglycerides (Fat)
 *Glucose (Sugar)
 CBC (Blood Count) -
 Hemoglobin
 Hematocrit
 WBC
 MCV (mean corpuscular volume)

*** List of all measures taken during the Cohort (date of measure and value)**

All other tests will list the most recent date of measure and value only.

Urine: Urine Protein
 Albumin

Will list the most recent date of measure and value only.

One graph that contains the following information:

Estimated GFR of all values over time
Blood Pressure history of all values over time
Weight of all values over time

Current medications listed on most recent F140
ABPM summary pages of the last ABPM will be printed by Study Coordinators and placed in folders.
Copy of last ECG
NIDDK certificate of appreciation

AASK Cohort Study Post Close Out 1/2 Visit Checklist

Activity	Completion Date	In Person/Phone call
Confirm final visit data collection complete		
Medication Prescriptions Given		
Medication Services Info pkt. Given		
Patient Handbook Provided		
Final Study Report Discussion		
Local MD Information Obtained		
Contact Info. Updated		
PI Meeting to review Health Status		
Exit Interview Conducted		
Gift/Certificate of Appreciation		
Copy of Report Given to Pt.		
Copy of Report/Letter sent to PCP		
Medical Care Confirmation		

**Final Data Collection Visit
March-June, 2007**

For Non-ESRD participants, refer to Table 1 or Table 2.

For ESRD participants, refer to Table 3 or Table 4.

For participants who have not been seen in 2007, refer to Table 5.

Non-ESRD Participants

Table 1: Used for Non-ESRD participants who have not had a C48 nor a C60 visit in its entirety in 2007.

Table 2: Used for Non-ESRD participants who have had a C48 or C60 visit in its entirety with confirmation of a successful echo, ECG, and ABPM in 2007.

ESRD Participants

Table 3: Used for ESRD participants who have not had a C48 nor a C60 visit in its entirety in 2007.

Table 4: Used for ESRD participants who have had a C48 or C60 visit in its entirety with confirmation of a successful echo and ECG in 2007.

Lost Participants

Table 5: Used for participants who have not been seen in 2007 and the center has used a search company or have a formal IRB letter stating that the site cannot search for the participant.

Table 1
Final Data Collection Checklist for Non-ESRD Participants
(Completed between March – June 2007)

*****All forms should be entered within 2 weeks of the visit.**

FORMS TO BE COMPLETED (listed in order of importance)	DONE (√)
*Form 144 – Hospital Admission Notification Form (<i>if applicable</i>)	
*Form 145 – Hospitalization Form (<i>if applicable</i>)	
*Form 122 - CBL Serum and Plasma Mailing Form (serum creatinine, etc.-fasting)	
<i>Form 124 - Central Serum and Plasma Results (Completed by CBL)</i>	
*Form 123 - CBL Urine Mailing Form (24-hr urine)	
<i>Form 125 - Central Urine Results (Completed by CBL)</i>	
*Form 110 - Blood Pressure Form	
*Form 111 - Visit/Missed Visit Form	
*Form 116 - Local ECG Form	
*Form 198 – Close Out Form	
*Form 199 – Post Close Out Form (<i>if applicable</i>)	
Form 85 - Exposures Data Form	
Form 105 - Pill Dispensing Form	
Form 113 - Local Lab Results: CBC	
Form 127 - CBL Dry Ice Mailing Form	
Form 140 - Medication Form	
Form 168 - CBL Nail Clipping Mailing Form	
Form 175 – Health Maintenance Questionnaire Form (<i>if not completed previously</i>)	
Form 180 - SF 36 Form	
Form 186 - Jackson Heart Study Approach to Life-A Form	
Form 187 - Jackson Heart Study Approach to Life-B Form	
Form 190 - Beck Depression Inventory-II Form	
Form 191 - Diener Satisfaction of Life Form	

***All forms that are listed above should be completed at the last data collection visit. However, if a participant will not allow all forms to be completed, the table lists the forms that should be completed in order of importance. The asterisked forms should be done prior to the others if needed.**

****If you did not obtain an ABPM, Echo or Central ECG at the last big visit (C48 or C60), try to obtain it at this visit.**

Table 2
Final Data Collection Checklist for Non-ESRD Participants
Who have completed a C48 or C60 visit in its Entirety
With confirmation of a Successful Echo, ECG and ABPM in 2007
(Completed between March – June 2007)

***All forms should be entered within 2 weeks of the visit.

FORMS TO BE COMPLETED (listed in order of importance)	DONE (√)
Form 144 – Hospital Admission Notification Form (<i>if applicable</i>)	
Form 145 – Hospitalization Form (<i>if applicable</i>)	
Form 122 - CBL Serum and Plasma Mailing Form (serum creatinine, etc.-fasting)	
<i>Form 124 - Central Serum and Plasma Results (Completed by CBL)</i>	
Form 110 - Blood Pressure Form	
Form 111 - Visit/Missed Visit Form	
Form 140 – Medication Form	
Form 198 – Close Out Form	
Form 199 – Post Close Out Form (<i>if applicable</i>)	

****If you did not obtain an ABPM, Echo or Central ECG at the last big visit (C48 or C60), try to obtain it at this visit.**

Table 3
Final Data Collection Checklist for ESRD Participants
(Completed between March – June 2007)

*****All forms should be entered within 2 weeks of the visit.**

FORMS TO BE COMPLETED (listed in order of importance)	DONE (√)
*Form 141 – ESRD Patient Hospitalization Form (<i>if applicable</i>)	
*Form 122 - CBL Serum and Plasma Mailing Form (serum creatinine, etc.-fasting)	
<i>Form 124 - Central Serum and Plasma Results (Completed by CBL)</i>	
*Form 111 - Visit/Missed Visit Form	
*Form 116 - Local ECG Form	
*Form 198 – Close Out Form	
*Form 199 – Post Close Out Form (<i>if applicable</i>)	
Form 85 - Exposures Data Form	
Form 113 - Local Lab Results: CBC	
Form 127 - CBL Dry Ice Mailing Form (<i>only if not collected prior to dialysis</i>)	
Form 129 - Follow-Up for Patients on Dialysis or Transplanted	
Form 140 - Medication Form	
Form 168 - CBL Nail Clipping Mailing Form	

***All forms that are listed above should be completed at the last data collection visit. However, if a participant will not allow all forms to be completed, the table lists the forms that should be completed in order of importance. The asterisked forms should be done prior to the others if needed.**

****If you did not obtain an Echo or Central ECG at the last big visit (C48 or C60), try to obtain it at this visit.**

Table 4
Final Data Collection Checklist for ESRD Participants
Who have completed a C48 or C60 visit in its Entirety
With confirmation of a Successful Echo and ECG in 2007
(Completed between March – June 2007)

*****All forms should be entered within 2 weeks of the visit.**

FORMS TO BE COMPLETED (listed in order of importance)	DONE (√)
Form 141 – ESRD Patient Hospitalization Form <i>(if applicable)</i>	
Form 122 - CBL Serum and Plasma Mailing Form (serum creatinine, etc.-fasting)	
<i>Form 124 - Central Serum and Plasma Results (Completed by CBL)</i>	
Form 111 - Visit/Missed Visit Form	
Form 129 - Follow-Up for Patients on Dialysis or Transplanted	
Form 140 - Medication Form	
Form 198 – Close Out Form	
Form 199 – Post Close Out Form <i>(if applicable)</i>	

****If you did not obtain an Echo or Central ECG at the last big visit (C48 or C60), try to obtain it at this visit.**

Revision of 01/30/2007

Table 5
Final Data Collection Checklist for Lost Participants
(Completed between March – June 2007)

Form 139 Reasons Patients Missed Visits Form

***Centers should use every effort to locate any lost participants.**

****Centers should only enter a Form 139 if they used a search company or have a formal IRB letter stating that the site cannot search for the participant.**