Manual 12
Quality Assurance and Quality Control
ARIC-NCS Visit 6

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Quality Assurance and Quality Control

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1. INTRODUCTION

1.1. Quality Assurance and Control Procedures

The distinction between quality assurance and quality control is both arbitrary and philosophical. The former is considered here as relating to activities to assure quality of data which take place prior to collection of data, while the latter relates more to efforts during the study to monitor the quality of data at identified points during data collection and processing. It is quality control on which this manual focuses, whereas quality assurance is the essence of the entire Manual of Operations, and includes the following activities:

1) Detailed protocol development. A clear description of the study design, training, certification, and the various data collection activities provides the blueprint for the study. Each protocol is a written reference for staff and researchers. Procedures for handling the routine, as well as the exceptional, are given. Those protocols constitute the ARIC-NCS Visit 6 Manuals of Operation.

2) Training. Training is the transfer of the study plans in the protocol to the research staff. The process has resulted in clarification and revision of the protocol. Special materials for this purpose have been developed for ARIC and are the basis for continuing education during the study.

3) Certification. Criteria to examine the adequacy of an individual's training have been established. Individuals meeting these criteria are qualified to execute a protocol or a segment of it. Certification indicates that an acceptable performance standard has been mastered or an adequate knowledge of material has been achieved. The Coordinating Center (CC) monitors the study to ensure that the research staff performs only those functions for which they are certified.

Quality control procedures involve monitoring data collection by observation (directly and by audio or video tape recording) and quantitative assessment (using repeated measurements and statistical analysis of study data). Monitoring is performed both by personnel within the field centers and when necessary by monitoring visits from the CC. A summary of selected aspects of ARIC Study quality control follows.

1) Observation monitoring. Over-the-shoulder observations of staff by supervisors are made to identify techniques that need improvement and points where the protocol is not being followed. Also, periodic monitoring visits by CC staff are made to observe clinic activities. Immediate feedback is given on issues related to protocol adherence, and recommendations for improvements are given to the field center Principal Investigator for action.

2) Quantitative monitoring. Repeat measurements taken by the same and different technicians are used as quality control tools. Randomly re-doing a fraction of an individual's work may not only stimulate better overall quality of data, but also allows estimation of measurement reliability. At the time of reporting the results of the study, it is important to establish that the “error” in the data is not so large as to threaten the validity of conclusions. In addition, descriptive statistics and graphical representation of study variables by technician and month are monitored to identify differences among technicians or trends over time.

3) Reporting results. Two aspects of the reporting of quality control monitoring should be emphasized. First, the results must be timely. When remedial action is required, reporting must be prompt so that a return to an acceptable level of performance is not

unnecessarily delayed. Second, the reporting format must be easily understood. Tabular presentations are accompanied by clear graphical displays.

4) Action on results. With conscientious and trained staff, quality control reports provide an opportunity to praise a job well done. On the other hand, a poor performance is the basis for some remedial action. Depending upon past performance, the amount of error, and the appropriate action may be a simple discussion to encourage a better performance. Re-training may also be appropriate at times.

1.2. Monitoring of Data Quality and Implementing Corrective Action

The subsequent sections of this Manual describe the reports used to monitor quality control. These reports are designed to be clearly understandable and to lead to corrective actions. A Quality Control Committee (QCC) is designated by the ARIC Steering Committee to coordinate and direct the quality control activities. This committee will have monthly conference calls to discuss issues that arise and review QC reports.

The QCC is charged with establishing the content of the quality control reports and reviewing them with specific attention given to deviation from protocols, and trends or shifts in data over time. The QCC prepares recommendations to the Steering Committee in matters of quality assurance, and contacts field centers, reading centers, or laboratories as needed, to advise them of a problem and to discuss the mechanism for correction. The QCC has representation from the CC, field centers, reading centers, laboratories, and NHLBI.

As the repository for ARIC Study data, the CC is responsible for preparation and dissemination of QC reports. These reports consist of tabulated data and summary statistics, and identify protocol deviations, recurrent problems, or temporal trends. Each field center and reading center is asked to respond to the reports and to implement corrective action. The distribution of periodic QC reports is as follows:

1) QC reports on technician-specific performance are sent to the respective field center principal investigators, to study coordinators and to the QCC.

2) QC reports on laboratories/reading centers' performance are sent to the respective principal investigators and to the QCC.

3) Summary QC reports are posted to the study website.

The following individuals should respond to the reports as follows:

1) Field center PIs, study coordinators: Review each QC report including technician-specific performance measures for their field center; identify a solution to each problem; implement corrective action; report corrective action to Coordinating Center QC Committee representative.

2) Laboratories and reading center directors: Review each QC report for their laboratory/center; identify a solution to each problem; implement corrective action; report corrective action to QCC.

3) Quality Control Committee: Review each QC report with attention to deviation from protocol, recurrent technician or field center problems, and temporal trends; contact field center, reading center, or laboratory investigators to review data quality problems and ensure solutions are proposed; monitor the implementation of corrective action.

4) Steering Committee: Review QC summary reports; monitor data quality trends; direct the QCC in areas needing special attention; propose changes to protocol when necessary.

1.3. Organization of the Quality Control Manual

What follows is a detailed list of quality assurance or quality control measures addressing each data transfer point or possible source of error. Section 2 describes certification procedures for field center staff. The ARIC study's system of making (blinded) repeated measurements for quality control purposes is used in so many areas of the study that a separate section is devoted to description of this topic (Section 3). Section 4 discusses the types and schedules of quality control reports and describes the analysis of study data for quality control purposes. Subsequent sections describe the quality control procedures for the various components of the data collection protocol.

2. CERTIFICATION PROCEDURES

Certification of study personnel is an essential aspect of effective quality assurance as well as quality control in clinical research. In order to maintain proper collection of data despite potential for personnel changes over the study period, the CC is responsible for establishing and providing the requisite minimum criteria and training and ensuring continued adherence to standards.

Although all ARIC staff members are expected to be familiar with the entire study protocol, the complexity of the design requires that study coordinators and staff designated to participate in certain areas of data collection for the study each be instructed and certified on specific data collection instruments and tasks.

Study coordinators are responsible for providing continuity from participant recruitment through exiting the study. Coordinators should be routinely involved in all aspects of the study with regard to participant and staff involvement as well as data collection. This includes recruitment and scheduling of participant visits as well as the performance (or supervision) of many segments of the clinic examination. Coordinators also serve as the liaison between their clinical center, laboratories, reading centers, and the CC. They communicate with participants' physicians when necessary with regard to study procedures and examination results. The study coordinator is responsible for accurate collection of data and oversight of the shipment of blood and urine samples to the Laboratories, and pertinent materials to the reading centers.

The responsibilities of study technicians can vary between field centers and with staff qualifications. The study coordinator is responsible for periodically monitoring the accuracy of the work done by auxiliary personnel. However, it should be noted that the Principal Investigator is ultimately responsible for the clinical behavior and ethical standards of all staff at his/her study center.

All study coordinators must attend the Central Training. This three-day training covers all aspects of the study protocol and is led by individuals with specific expertise in the given exam component. Attendance at the centralized training is strongly encouraged for all study personnel.

In addition, staff must be certified in the following areas in order to collect such data. Specific criteria and requirements for training in these areas are described in detail in the following sections of Manual 2 (unless otherwise specified):

A. Informed Consent

B. Anthropometry

C. Seated Blood Pressure

D. Biospecimen Collection & Processing

E. Interviewing techniques
F. Neurocognitive Test
G. Neurologic interview
H. Medication Coding
I. Physical Function
J. Peripheral Neuropathy
K. Zio®XT Patch
L. Audiology
M. Physical Activity/Falls

Study technicians may train and be certified in any of the areas to which they have been assigned by their Principal Investigator (PI) or Study Coordinator. Certified Study Coordinators or lead personnel may train and certify new personnel on site after initiation of the study by following the guidelines specified in Manual 2 and certification procedures described below. It should be noted that the Study Coordinator remains responsible for all data collection, data entry, and other procedures that may be delegated to staff. Study Coordinators should frequently monitor staff members to ensure the high quality performance of all procedures.

Study Coordinators will submit a Certification Request Form (Appendix 11) to the CC to document that a staff member has completed the necessary requirements for certification. The Certification Request Form documents how, when and which procedures/interviews were certified. The CC will assign a staff code number upon receipt of this form. Should staff learn more procedures and interviews for certification since the initial certification request, a re-submission of the form is needed to update those new areas of certification.

The CC will continually update records of all certifications at each study center, and staff code numbers will be compared against the data collection forms to ensure that only certified staff perform data collection on the specific procedures/interviews to which they have been assigned. Additional training and supervision will be carried out as individually needed at the field centers. Continued supervision will be the responsibility of the Study Coordinator. If at any time a center is found to be lacking in certification requirements, or the quality of data collection is found to be less than optimal by the Quality Control Committee, the center will be notified. If the center does not institute corrective action in the time allotted, further follow-up will take place by staff charged with study administration in an attempt to resolve the issues.

3 QUALITY CONTROL SYSTEM FOR REPEATED MEASUREMENTS

To estimate the reliability of laboratory and body composition measures, some participants will provide an additional sample of blood or urine, or will have anthropometric measurements repeated by a second technician at the same visit. The repeated anthropometric measurements are recorded on a new or second “occurrence” of the Anthropometry (ANT) form in the DMS for the participant that is having the measurement repeated. QC laboratory specimens are labeled with a phantom participant ID that is indistinguishable in format from other ID numbers, so that the laboratory is blinded to the QC process.

The Phantom Form (PHT) is used enter the phantom ID to the matching ARIC participant IDs contributing repeat measurements. The Phantom Form is entered into the DMS in the same

way as regular study data (see Manual 7 for more information). The QC phantom participant folders are created as follows:

1) Affix a phantom ID label to the Phantom Tracking Sheet; place these in a folder.

2) Every time a participant contributes replicate data, his/her ARIC participant ID is affixed to the Phantom Tracking Sheet next to the type of data that was contributed and the data should be entered into CDART using the PHT form. Seven individuals will contribute to each Phantom Tracking Sheet.

3) After completing the Phantom Tracking Sheet for the seven phantom IDs, the folder is processed along with the regular stream of participant folders as if the Exit Interview had just finished

4. ANALYSIS OF STUDY DATA FOR QUALITY CONTROL PURPOSES

The methods to monitor the quality of the ARIC data collection process include analyses of the study data itself, overall, by center, and by technician. There will be periodic reporting by field center on:

1) status of variables in the database (no problem, skipped due to skip rule, problem with the entry), to assess the prevalence of data entry problems,

2) distribution of categorical (frequencies) and continuous variables (means, standard deviations, percentiles),

3) distribution of variables that give information on protocol adherence and the validity of data (e.g., fasting time before blood drawing).

4.1. Quality Control Reports

For a report to be of use in correcting problems, it must appear frequently and reflect as much of the collected data as possible. The frequency of reports is determined by balancing the study's need for prompt and frequent monitoring with the available resources to generate such reports and the need to accumulate enough data to have an adequate sample size. For example, analysis of adjusted means by technician is not feasible on a monthly basis, but can usefully be done each quarter. The standard monthly QC reports will contain the following information:

1) Repeated measures

   Anthropometry

2) Descriptive statistics

3) Timeliness and completeness of data entry

4.2 Replicate Data Analysis

The following modeling process will be used to analyze replicate QC data. The total variance of the study data (σ_T^2) can be partitioned into two components: the measurement error component (σ_e^2) and the true variation between and within individuals in the study population (σ_b^2), so that $\sigma_T^2 = \sigma_b^2 + \sigma_e^2$. One quantity of interest for assessing data quality is the reliability coefficient, $R = \sigma_b^2 / \left(\sigma_b^2 + \sigma_e^2 \right)$, which is one minus the proportion of total variance due to error variation. The components of variance will be estimated from the replicate data using maximum likelihood (ML) or restricted maximum likelihood (REML) methods.

The estimates of reliability and error variance will be closely watched. In monitoring biospecimen data, $\hat{\sigma}_e$ for each assay is compared with the target standard deviation (SD) which the laboratory has set based on analyses of internal quality control pools. Blind replicate estimates which are more than twice the target SD are considered cause for concern. In addition, if the coefficient of variation (CV) is greater than 10% corrective action should be requested from the laboratory.

To monitor for systematic differences between original and replicate measurements, the proportion of non-zero differences which are positive is monitored. With no systematic trend, this proportion should be one-half. A sign test is done to test for significant differences, and significant differences which persist over several months are pointed out to the laboratory. Means and percentiles of these differences are also presented.

Before any analysis is done on the QC replicate pairs, the data are screened for possible mismatches or "strange" observations. For each biospecimen, the mean and standard deviation of the difference between repeat and original pairs are used to determine acceptable intervals.

5. ANTHROPOMETRY

5.1. Anthropometry Procedures

Anthropometry is performed with the participants wearing light clothing, a scrub suit or an examination gown. The measurements include body weight, bioimpedance and waist and hip girth. Weight is measured without shoes. Important quality assurance/control measures include clear and detailed protocols for each measure, training and certification, instrument checks, replicate measurements, observation of technicians by a supervisor, and a periodic quality review of study data by the QCC.

5.2. Training and Certification

All data collectors taking anthropometric measurements must be certified by successfully completing training requirements. Training and practice sessions will be conducted prior to certification. An examiner who attends the central training and passes certification criteria can train and certify other examiners at the field center. Certification testing requires a minimum of 5 practice subjects be measured by both the expert trainer and the trainee. Agreement between the expert and the trainer must be within 0.5 kg for weight, and 2 cm for hip and waist measurements for at least 4 of the 5 subjects.

5.3. Observation of Anthropometry Measurement

Technicians are observed by the study coordinator twice monthly for the first month following a technician's certification and then twice per year to ensure standardization. The Checklist for Observation of Anthropometry Measurements (Appendix 3) is used to document these observations and deviations from the protocol are reviewed with the technicians. The observations are also summarized quarterly on the Summary of Observation and Equipment Checklists (Appendix 1). A minimum of 6 procedures every month is required in order to maintain certification. Local re-training sessions are scheduled when a lack of standardization (e.g., technicians who fail to meet the certification criteria described above) is observed among the technicians.

5.4. Maintenance of Equipment

Anthropometry equipment is calibrated frequently and results are recorded on an Anthropometry Equipment Calibration Log (Appendix 7). Scales are zero balanced daily and calibrated weekly, or when moved. Place the 10 kg calibrated weights on the scale and read the result when the digital display has stabilized. The values should be within 1.5 kg of the expected weight. If it

weighs outside this range, notify the study coordinator to have the scale recalibrated by the manufacturer or by the appropriate institution personnel. These equipment checks may be done by any certified anthropometry technician. Quarterly, the equipment logs are summarized onto the Summary of Observation and Equipment Checklist (Appendix 1), which is then sent to the Coordinating Center. Copies of the equipment logs may be requested by the Coordinating Center.

5.5. Random Replicate Measurements

Five percent of participants will be randomly selected to have anthropometry measurements repeated by a different technician. The steps in the random selection and repeat measurement process are:

1) When the ANT form is opened item 11 will automatically be populated with either "Selected for ANT QC" or "Not Selected for ANT QC"

2) The technician performing the initial measurements should not be made aware that a repeat is to be done until after the initial measurement is complete.

3) The repeat measurements should be done as soon as they can be fit in to the participant's and technician's schedules. When more than one trained technician is available, the repeat measurements should be assignment randomly to one of the certified technicians, say, by coin toss.

4) The technician who repeats the measurements completes a new or second occurrence of the Anthropometry form, without looking at the measurement determined by the first technician. Instructions on how to key a second occurrence of a form are available on the ARIC website under TRAINING --- DMS. For questions please contact the Help Desk.

Inter-technician agreement is analyzed by the QCC and serves as a criterion for recertification. Retraining sessions are scheduled at the request of the Quality Control Committee when a lack of standardization is observed among the technicians.

6. SITTING BLOOD PRESSURE

The OMRON HEM-907XL sphygmomanometer is used to measure seated blood pressure. The technician explains the procedure to the participant, measures arm circumference, wraps the arm with the correctly-sized cuff, and records the average of the three readings after the participant has been seated quietly for 5 minutes. Important elements in quality assurance are training and certification programs, observation of data collection by the study coordinator, quarterly simultaneous blood pressure measurements by the technician and the study coordinator, and standard equipment maintenance procedures performed and summarized quarterly onto the Summary of Observation and Equipment Checklist (Appendix 1) and sent to the Coordinating Center. The CC will also monitor the distribution of readings from the OMRON to look for any irregularities.

6.1. Training and Certification

Blood pressure technicians are trained and certified at the central training session, or at local field centers by a certified technician. Certification results from training of new staff at the field centers are submitted using a Certification Request Form (Appendix 11) to the CC to document certification status.

Certification for sitting blood pressure requires the trainer to observe the trainee performing blood pressure measurements on 3 volunteers to look for adherence to protocol procedures. Results are summarized onto the Checklist for Observation of Blood Pressure Measurements (Appendix 4). A technician who attends the central training and passes certification criteria can train and certify other technicians at the field center.

6.2. Observation of Blood Pressure Measurement

Quarterly, the blood pressure supervisor observes each technician responsible for taking blood pressure measurements using the Checklist for Observation of Blood Pressure Measurements (Appendix 4).

6.3. Maintenance of Equipment

1) Availability of all sizes of cuffs: The blood pressure supervisor makes certain that the field center always has the full range of 4 blood pressure cuffs available at each blood pressure station. Field center staff report immediately to the supervisor if they cannot find all cuff sizes at the station.

2) OMRON sphygmomanometer: Each OMRON unit is checked every 3 months as described in Manual 2. The results of the calibration checks are recorded on the OMRON calibration log (together with the unit number, the date and the technician ID) and sent to the Coordinating Center for inclusion in the quality control reports. A sample copy of the maintenance and calibration log is found in Appendix 10. Quarterly, the equipment logs are summarized onto the Summary of Observation and Equipment Checklist (Appendix 1), which is then sent to the Coordinating Center.

7. BIOSPECIMEN COLLECTION AND PROCESSING

7.1. Blood Collection and Processing

At the time of the telephone contact, participants are requested to fast for 8 hours before the field center visit unless they are diabetics taking insulin or have other medical reasons that make fasting inadvisable. The specific steps to be taken in blood drawing and processing are described in Manual 2. Blood samples are shipped frozen on dry ice bi-weekly to the ACRL Central Laboratory and the UMN laboratory. All shipments to the laboratories are made by courier for overnight delivery services. These steps are performed by technicians trained in the ARIC protocol and certified to have adequately mastered its details.

The first step in quality assurance for blood drawing is the training and certification process. Other steps include maintaining logs of equipment checks, observation of technicians (by other technicians and by CC staff on monitoring visits) as they go through the sequence of steps in blood drawing and processing; review of the condition of samples received at central laboratories for problems in shipment; and periodic analysis of the study data for participant compliance with fasting and for signs of problems in drawing or processing, such as hemolysis or delays in completing processing.

Quarterly, the supervisor observes each technician responsible for collection, processing, and shipping of the bio-specimens using the checklist given in Appendix 5. These observations are summarized quarterly on the Summary of Observation and Equipment Checklists (Appendix 1).

7.2. Training and Certification

To be certified, technicians complete central training taught by certified laboratory staff which includes biospecimen (blood, urine) collection, processing, packaging and shipping as well as quality control measures such as phantom specimen collection. Each technician must complete

the training and pass both written and practical exams before becoming certified for the ARIC study. Certification requirements for personnel who do not attend the centralized training are:

- Collection, processing, and shipping specimens for 3 volunteers under the supervision of the certified lead technician at the field center, and
- Completion and submission to the CC of the written exam (Appendix 9)

Only certified phlebotomists should be hired. ARIC training is specific to the collection and processing procedures of the study.

7.3. Maintenance of Equipment

Each field center performs daily temperature checks on the refrigerators, freezers and the refrigerated centrifuge as well as the rooms in which these are located. The actual speed of the centrifuge is checked and recorded annually with a tachometer. The results of these checks are recorded on the Daily Centrifuge, Freezer, Refrigerator and Room Temperature Log (Appendix 8) kept at the blood processing station, and are summarized onto the Summary of Observation and Equipment Checklist (Appendix 1) quarterly and sent to the Coordinating Center.

7.4. Monitoring by the Central Laboratories

The laboratories review the drawing and processing time, as recorded on the Biospecimen Collection Form. If there are extreme values that raise questions about the validity of laboratory results, the field center is alerted to the problem. If a value is considered suspicious or an "outlier", the Biospecimen Collection Form is reviewed for any collection/processing discrepancies, and if there are concerns related to the collection/processing time the field center is notified by the lab. Monitoring is described in more detail in the laboratory manual.

7.5. Packing Samples for Shipment to the Laboratories

All vials of blood samples as well as the plastic bags in which the samples for a given participant are packed for shipment to the laboratories are labeled with both the participant and the laboratory ID. To avoid delays in transit to the laboratories which might cause samples to be warmed or thawed in shipping, all samples are shipped by an overnight delivery service. All frozen plasma, sera, packed cells, urine, and Paxgene tubes collected and stored within the last 2 work weeks are shipped to the laboratory on Monday. Samples can be shipped on Tuesday if the Field Center is closed on Monday, but the contact person at the laboratory must be notified that the shipment will arrive one day later than usual.

A shipping list is enclosed with each shipment to the laboratories giving the IDs for all sets of samples that are enclosed (see Manual 7). A pick-up will be made by UT Genetics Laboratory from the ACRL. The person unpacking these samples at the laboratory verifies that the IDs on the vials match the ID on the plastic bag and checks both against the shipping list(s). If any discrepancies are detected, the laboratory will contact the field center(s) to resolve the problem.

Blood vials shipped to the laboratories must be packed securely to avoid breakage and warming. Full instructions for packing samples are specified in Manual 7. The laboratories monitor the arrival condition of the samples sent from each field center on the Shipping Form. If problems are encountered, the laboratories notify the Field Centers involved. If a pattern of sample damage becomes apparent that suggests a need to modify the materials used to ship samples (e.g., excessive leakage of a certain type of vial) or how samples are packed, the QCC should be alerted to ensure appropriate action is taken.

7.6. Urine Collection and Processing

After a participant is greeted at the clinic, he/she is asked to provide a urine specimen at the participant's convenience. When the participant is ready to void, a specimen cup (labeled with the participant ID) is provided, and the participant is instructed to fill the cup if possible. If the

sample is insufficient for processing, the participant is requested to void again in a clean container prior to leaving the field center. Prior to processing, the technician records on the Biospecimen Collection Form whether a urine sample was obtained, the collection time of the initial (if more than one) urine sample, and adequacy of volume.

7.7. Replicate Blood and Urine Specimens

Repeat samples are collected for 8 blood specimens and a urine sample. A replicate sample is obtained by either drawing 1 to 2 additional tube(s) of blood, or by dividing a urine sample into separate containers. The replicate samples are then processed using the same method as for the original samples. Over the entire study, replicate samples will be obtained on 5% of all specimens (n ~ 200 if the target of 4214 participants are examined). Thus, 33% of participants (n=1400, or 7×200) will contribute to the pool of replicate specimens. Repeat samples will be collected over the duration of the study. Ongoing monitoring of the quality of replicate biospecimen data will be conducted by the Coordinating Center and adjustments to the number of participants needing to provide replicate data will be made as needed. The extra specimen(s) will be labeled with a Phantom ID. Each month, the Coordinating Center reviews the number of QC phantom forms completed to ensure the procedures for obtaining replicate samples is being followed.

A replicate urine sample requires that the participant provide at least 10 mL of urine. Urine is divided among six 2.0 mL (1.5 mL per vial) vials to be used for determination of creatinine and albumin levels by the UMN Laboratory, as well as reserved for future testing (see Manual 7 for details). To reduce the chance of error in linking the real participant ID with the phantom ID, as soon as a replicate sample is obtained the real participant ID label and the phantom ID labels should be affixed to the appropriate space on the Phantom Tracking Sheet.

8. BIOSPECIMEN PROCESSING AT THE LABORATORIES

8.1. Procedures for Laboratory Analyte Determinations

Blood samples are collected and processed at the field centers for shipment to a laboratory for analysis of several analytical tests. In the present section, the emphasis is on quality assurance in the central laboratories, beginning with the receipt of samples. This section differs from other chapters of this manual in being more of a general overview and summary of quality assurance measures. These matters receive careful and detailed discussion in the laboratories manual, which covers procedures for: receiving samples and storing them at a proper temperature until analysis; schedules of equipment maintenance; storage and handling of reagents, calibration standards, and quality control materials; internal and external quality control programs; and transcription and reporting of measurement results. This section of the manual supplements the laboratory manual by its discussion of reporting on the effectiveness of laboratory quality assurance procedures and of the utilization for quality control of (1) analyses of study data and (2) blind replicate samples from participants sent to the laboratory.

8.2. Receiving Samples at Laboratory

At the laboratories, a record in the local data base is created using the participant ID number for each specimen when it arrives. It is important in handling ARIC frozen blood samples to avoid any unnecessary exposure to room temperature. Clear procedures for unpacking specimens upon arrival are set out in the laboratory protocols to minimize such exposure. While awaiting analysis, specimens are to be kept in storage at -80^0C. The laboratory has provisions for (1) prompt detection of power failure or of failure of a freezer to maintain the proper temperature, including both local alarms and alarm signals to a central security office that will notify appropriate laboratory personnel if a problem develops after hours; (2) back-up power supplies

in the event of power failure; (3) plans for the use of dry ice to maintain the sample temperature until any problems with the freezer can be repaired.

The probable stability of different analytes in frozen storage has been assessed and standards set for how soon analyses will be performed after the arrival of specimens at the laboratory.

8.3. Maintenance Procedures at the Laboratories

Maintenance procedures for laboratory equipment are fully specified in the laboratory protocols or in manufacturers' manuals referenced in the protocols. Technicians are fully instructed in these procedures.

A regular schedule is set up for routine maintenance procedures, with logbooks kept on their performance. The laboratory supervisors review these logs on a regular basis to verify that proper maintenance procedures are being carried out according to the schedule set and that any special maintenance procedures needed are carried out.

The laboratory protocol fully specifies the reagents used, the sources from which they are procured, and the procedures used to prepare and store reagents to guarantee the stability of the reagent and the accuracy of the assay. The laboratory protocol also fully specifies the sources of calibration standards and quality control materials, the procedures used to prepare and store calibration standards and quality control materials, to guarantee the stability of the material and the accuracy of the assay. To maintain the comparability of measurements using new and old calibration standards and controls, an overlap period is carried out, during which concentration values for the new standard are determined using the standard which is being replaced.

8.4. Internal Quality Control Pools

The laboratories maintain an internal quality control program involving the analysis of multiple samples from quality control pools in each analysis run in which ARIC study samples are analyzed. Results for these samples are used to decide whether the measurement process is in control and whether the results on the study samples will be accepted or whether the measurements should be repeated after taking corrective action. Quarterly, the laboratories provide a summary of the internal quality control results to the Coordinating Center, including the following information for each assay: (1) monthly summary statistics (n, mean, and standard deviation) on all quality control pools, including new pools being overlapped to replace established QC pools; (2) summaries of any unusual problems or conditions noted. The Coordinating Center reviews these reports for evidence of trends with time in results on these pools.

Results on analyses of quality control pools are analyzed by the Coordinating Center for trends over time that may represent either (1) shifts in measurement or (2) changes over time in the concentration of the analyte in a given pool. To determine which of these is the case, trends in a given pool can be compared with (1) trends in other pools (if any) used to control analyses of a given analyte; (2) trends in differences on measurements of samples from quality control phantom participant duplicates which are repeated several months apart; (3) trends in the study data. If there is evidence of changes in the concentration of a control pool over time, it should be replaced.

8.5. External Quality Control

For many of the assays performed in the ARIC study, the laboratories participate in various standardization or certification programs run by outside agencies, such as the College of American Pathologists or the CDC Lipid Standardization Program. The laboratories should continue to maintain acceptable results in these programs and promptly provide the Coordinating Center with copies of any reports on their performance generated by these

programs. Should any of the results achieved in these programs appear problematic, they are reviewed by the Coordinating Center and the Quality Control Committee or Laboratory Committee together with other quality control information on the assay in question to determine what action is appropriate.

9. PARTICIPANT INTERVIEW

Establishing quality control for interviews is critical in ascertaining whether interviews are conducted according to protocol. If interviews are not uniformly conducted according to protocol, then differences in the information obtained from participants may merely represent differences in technique between interviewers. Audio recording and observation are used to monitor the quality of the data that interviewers collect as described below.

9.1. Certification on Interviewing Techniques

Requirements for certification or re-certification on general interviewing techniques include:

- Attending central training, or reviewing a presentation on General Interviewing Techniques (on study website).
- Successfully completing a short written exam on material, for initial certification. Completed written exams are sent to the CC for evaluation.

9.2. Observation of Interviewing Technique

Quarterly, the supervisor will observe each interviewer while an interview is in progress. Interviewers will not know in advance which interviews will be monitored for quality control purposes. The supervisor will rate the interviewer's performance using standard criteria from the Checklist for Observation of Interviewing Techniques (Appendix 2) and give the interviewer immediate feedback. Quarterly, these interviews should be summarized on the Summary of Observation and Equipment Checklists (Appendix 1). Complete the Checklist for Interviewer Recertification (FIR).

9.3 Quality Control

Selected interview data will be included in the quality analyses report periodically evaluating patterns by interviewer ID in some key responses and missing observations. If the QC analyses suggest potential problems the QC committee recommends audio-recording the some of the general interviews.

9.4 Survey Instruments

A survey instrument is a tool for consistently implementing a scientific protocol for obtaining data from respondents. The survey instrument includes questions that address specific study objectives. Certification on survey instruments requires attendance at the training webinar or review of webinar training slides for local training.

10. Neurocognitive Test

A battery of neurocognitive tests that measure global mental status (MMSE) and three specific cognitive domains (memory, language and executive function) will be administered.

10.1. Training and Certification

Prior to the examination, examiners will be trained centrally to a common level of proficiency in the administration and scoring of the neurocognitive measures. Following central training, examiners will upload audio-taped neurocognitive assessments (the measures are found in the

NCS cognitive testing packet) and associated paper forms to a designated location on the ARIC website for review by an investigator on the Neurocognitive Committee. Certification assessments should not be performed on ARIC participants. Examiner certification for the neurocognitive exam is achieved by review and approval of performance by the neurocognitive expert.

Following central training: New examiners will submit 3 audio-taped neurocognitive assessments and a PDF of each Neurocognitive Booklet (and relevant scoring materials) prior to start of V6. Examiners who were previously certified to perform the neurocognitive assessment at Visit 5 will submit 1 audio-taped assessment and a PDF of the Neurocognitive Booklet (and scoring materials) prior to V6.

The field center lead examiner or study coordinator is responsible for the basic training of all new field center examiners hired after central training. Following basic training and approval by the field center study coordinator, new examiners will submit 3 audio-taped neurocognitive assessments for review and approval.

Maintaining proficiency in the administration of the neurocognitive measures requires regular exposure to the protocol. In order to maintain certification, primary examiners will administer the neurocognitive measures at least 4 times per month. Quarterly, these reviews are summarized onto the Summary of Observation and Equipment Checklist (Appendix 1), which is then sent to the Coordinating Center

10.2. Audio-recording of Neurocognitive Component of Interview

Audio-taped sessions and associated documentation for each examiner should be submitted for reviewed by a neurocognitive expert to ensure appropriate pacing, adherence to protocol, and accuracy of recorded responses. Notes about any inconsistencies will be relayed to the study coordinator. The schedule for QC recordings is as follows: 2 in the first month of the study followed by 1 recording every other month thereafter until the end of the study. Sites should upload two audio recording in September 2016 and then followed by one recording in November 2016, January 2017, March 2017, May 217, July 2017, September 2017 and November 2017. General feedback that pertains to all examiners will be provided on QCC conference calls. These calls will also provide an opportunity to discuss and problem-solve various exam issues that may arise.

Table 10.2 Interview components to be recorded

Component	Form Acronym	Interview component
Neurocognitive	MME	Mini-Mental State Exam
	NCS	Neurocognitive test battery
Neurologic	CDI	CDR-Informant Interview
	CDP	CDR-Subject Interview

10.3 Instruction for recording on OLYMPUS DM-520 Digital Voice Recorder

The Olympus DM-520 recorder uses rechargeable batteries that allow at least 24 hours of use in recording mode. The batteries can be charged by connecting the device into a computer

USB port using the cable provided. By default, the DM-520 records at 100% volume level to prevent accidentally recording with the volume set too low. Microphone sensitivity can be adjusted via the MIC SENSE option in the recorder's menu (see next paragraph for instructions on changing device settings).

Record using MP3 (MPEG Audio Layer-3) format at a bit rate of 192 kbps. Approximately 46 hours of audio can be recorded at this setting. A microSD card (up to 16 GB) can be purchased and installed into side slot to increase this capacity. The devices should be preset with these settings, but if you need to modify: press the **MENU** button for 1 second or longer, then press the **–** button to get to the Rec Menu, and then press the **OK** button. At the Rec Menu, press the **–** button to get to Rec Mode and then press the **OK** button. Choose MP3 and 192 kbps.

Step 1: Turn the recorder on. If you are not at the Home Screen, Press the **Home** button and select **Recorder**.

There are 5 possible recording folders that each hold up to 999 files. For ease of finding files, each interviewer should be assigned a specific folder for use throughout the study. Note, however, that more than one interviewer can be assigned to the same folder.

Step 2: Select the staff-assigned recording folder using **+** or **–** button.

Step 3: Press the **REC** ● button on side of recorder to start recording. The recording indicator light glows and [●] appears on the display.

Step 4: The interviewer dictates 4 items before beginning the interview:

- Name and Staff Code number
- Interview component (General Interview, Neurocognitive, Neurologic)
- Participant ID number
- Date

Step 5: Press the **SCENE** button at the end of each questionnaire to create and index marks, or digital tags, to allow the user to easily skip forward or backwards in a single file to listen to a particular questionnaire.

Step 6: Press **STOP** button on side of recorder to stop recording.

Separate digital files are used to record each interview component listed in **Table 10.2** for a given participant. The exception may be if multiple interviewers administer the set of questionnaires to a participant.

10.4 Instructions for downloading digital recordings to your computer.

Step 1: Turn the recorder on. If you are not at the Home Screen, Press the **Home** button and select **Recorder**.

Step 2: Connect the USB connection cable to the USB port of your computer, then connect the USB cable to the bottom of the recorder.

Once connected, the Windows Autoplay feature will give you the option to Open Folder to View Files using Windows Explorer. Once you select this option, you will be taken to the device drive name, usually DM_520 (D:). If you do not get this option, simply open My Computer to see the device drive.

Step 3: Select the **Recorder** folder. Copy folders A-E the file to a known location on your computer. Rename the files using naming convention that identifies the staff ID of the interviewer, the date of the interview and the content. The date is specified in YYYY-MM-DD format so that it is easy to find when sorted alphabetically. The label/name of the recorded file(s) should look like:

File name	Center+Staff ID	Date (YYYY/MM/DD)
M313_2011-08-20_Neurocognitive	M313_	2011-08-20
W429_2011-08-20_Neurologic	W429_	2011-08-20

Step 4: Delete folders A-E in the Windows Explorer window. Note these folders will get recreated on the recorder.

Step 5: Leave your recorder connected until fully charged. When you want to disconnect the device, click on the "Safely Remove Hardware" icon of your task bar. From this dialog you can click on the device you want to remove, and press **Stop**. Once Windows is done with it, you can then remove the device.

10.5 Review of the recordings by the supervisor

Audio-taped sessions and associated documentation for each examiner should be submitted for reviewed by a neurocognitive expert to ensure appropriate pacing, adherence to protocol, and accuracy of recorded responses

10.6. Instructions for Uploading Audio Files for Review

Digital audio recordings are reviewed after uploading them to the secure portion of the study website (http://www2.cscc.unc.edu/aric/) and, select Cohort → Audio .

TO UPLOAD AUDIO FILES

The digital recordings are named following a standard naming convention: field center letter, staff ID, date (in YYYY-MM-DD format) and the interview component as described in the previous section and shown here: ***W406_2010-10-23_Neurocognitive***

TO UPLOAD AUDIO FILES

TO UPLOAD AUDIO FILES

Step 1: Login to the Study website (http://www2.cscc.unc.edu/aric/) and, select Cohort → Audio. **Step 2:** Select the "Upload" link in the top right of the screen.

Step 4: Enter information required by fields as follows:

a. *Title*: Type the name of the file (or copy the filename after loading)

b. *Date*: Put the date included in the file-name.

c. Click 'Choose File' beneath 'Add a new file' and browse to open the file to upload. Click 'upload.'

d. Select the Audio File Category among the following options:
"Neurologic"
"Neurocognitive"

e. Select your Field Center

f. Scroll to the bottom of the page and click 'Save.'

Step 5: Verify that your files have been uploaded by going back to the Cohort → Audio page.

10.7. Instructions for listening to the audio files

1. Login to the Study website (http://www2.cscc.unc.edu/aric/) and~~.~~ select Cohort → Audio
2. Click beside the music icon for the digital recording you wish to listen to. Windows Media player should open.
3. Click beside the PDF icon to view the documentation associated with the audio file.

10.8 Newly hired interviewers

The above QC protocol for recording and reviewing to audio-recorded interviews applies to interviewers newly hired in the course of the study.

10.9. Analysis of Study Data

Study data will be analyzed periodically to assess frequency of interviews for each interviewer, for each questionnaire. Minimum levels will be set to allow for continued certification. Levels of missing data will also be assessed by interviewer, and maximum acceptable levels set.

11. Neurologic Interview

11.1 Training and Certification

Study nurses are trained and certified at a central training session or at a local field centers by certified technicians prior to administering the neurologic exam on a participant. Training involves instruction on general interviewing techniques, review of each exam component (forms and QxQ instructions, manuals, and discussion of challenges to data fidelity.

Online training and certification for the CDR is required (www.adrc.wustl.edu). After selecting "Begin CDR Training", the user will be asked to register after which they will have access to 9 videos, each approximately 30 minutes in duration. The trainee should plan to review these videos over several days.

Two audio-taped recordings of the CDR interviews (Informant and Subject interviews) and associated documentation (CDR-informant, CDR-subject, and CDR-Summary forms) per trainee, will be reviewed by a study neurologist for certification.

For staff who previously were certified in the CDR for visit 5, the online training does not need to be repeated. Instead, two audio-taped recordings and their accompanying documentation are needed to be uploaded for re-certification, after in-person training is completed.

Maintaining proficiency in the administration of the neurologic measures requires regular exposure to the protocol. In order to maintain certification, primary examiners will administer the neurologic measures at least 4 times per month. Quarterly, these reviews are summarized onto the Summary of Observation and Equipment Checklist (Appendix 1), which is then sent to the Coordinating Center

11.2. Audio-recording of CDR and Neurologic Interviews

Neurologic interviews (to include the neurologic history, and the NPI for the informant interview) should be audio recorded for certification, with accompanying documentation as well. These audio-taped sessions and associated documentation for each examiner should be submitted for

reviewed by a neurocognitive expert to ensure appropriate pacing, adherence to protocol, and accuracy of recorded responses. Notes about any inconsistencies will be relayed to the study coordinator. The schedule for QC recordings is as follows: 2 in the first month of the study followed by 1 recording every other month thereafter until the end of the study. Sites should upload two audio recording in September 2016 and then followed by one recording in November 2016, January 2017, March 2017, May 217, July 2017, September 2017 and November 2017. General feedback that pertains to all examiners will be provided on QCC conference calls. These calls will also provide an opportunity to discuss and problem-solve various exam issues that may arise.

11.3. Uploading Audio-recordings

Examiners should provide audio recordings and corresponding PDFs of the following testing items:
-Testing packet
-Neurocognitive scoring summary form
-Trails A & B
- Digit Symbol Substitution form
- Incidental Learning form
- Intersecting Pentagons (from the MME)

In addition, those interviewers conducting the neurologic interviews and the CDR should upload audio recordings and the corresponding PDFs also to the same location on the ARIC website.

12. MEDICATION TRANSCRIPTION

12.1. Training and Certification

The Medication Survey (MSR) records all prescription and over-the-counter medications, including cold and allergy medications, vitamins, herbals or supplements used by participants in the four weeks preceding their interviews. The survey ascertains usage of up to 25 medications. Ascertainment includes scanning of twelve-digit Universal Product Code (UPC) bar code symbols when available. Medical Therapeutic Classification (coding) is automated where possible. Otherwise, manual coding is centralized (performed only at the Coordinating Center).

Interviewers are centrally trained and when certified, assume responsibility for providing local staff training in medication scanning / transcription.

Interviewers are certified to administer the MSR by attending the central training, completing the scanning / transcription exercise designed by the central trainer, and passing with a score of ≥ 80%. New staff unable to attend central training are eligible for remote certification when:

- The candidate is trained by the lead certified interviewer at the corresponding Field Center.
- The Coordinating Center has sent to the Study Coordinator mock medication with detailed instructions for the candidate's certification.
- The candidate independently completes an MSR and enters it into the CDART1 training system.
- The Study Coordinator informs the Coordinating Center for evaluation. The candidate passes with a score of ≥ 80%.

- The candidate completes five interviews demonstrating adequate technique based on review and approval by the lead interviewer.
- The Study Coordinator submits a request for certification to the Coordinating Center on behalf of the candidate.

12.2 Quality Control

With a participant's approval, interviews maybe audiotaped for quality control. The Coordinating Center may perform site visits to observe technique and adherence to protocol. The Quality Control Committee monitors data quality semi-annually.

13. Physical Function

The measures of physical function include the Short Physical Performance Battery (SPPB) which consists of chair stands, a regular paced 4-meter walk, and balance tests, as well as grip strength.

13.1 Training and Certification

A training video for the SPPB is available online. Instructions for downloading the video ("Instructions – pdf ") and the demonstration video ("CD (Download and Execute – (.exe)) can be found at http://www.grc.nia.nih.gov/branches/ledb/sppb/index.htm. This video should be reviewed prior to initial training session and every 6 months. Interviewers can be trained centrally or locally. Training includes:

- Watch the video for the SPPB
- Read and study the QxQ
- Attend ARIC training session on performance test administration techniques, or be trained at the ARIC field center by an experienced examiner
- Practice on other staff or volunteers
- Discuss problems and questions with local expert or QC committee

Certification will include:

Complete training requirements

- Recite exclusions
- Conduct exam on two volunteers:
  - According to protocol, as demonstrated by completed QC checklist
  - Times agree within ± 0.5 second of QC officer or designated personnel for SPPB and 5 seconds for 2-minute walk.

The following elements must be demonstrated successfully for certification:

Chair stands

- Back of chair against a wall
- Script correctly and clearly delivered
- Correctly demonstrates two stands, emphasizing full stand and return to complete sit
- Says "Ready? Go" for each test
- Records timed measure within 0.5seconds of QC officer or designated personnel
- Counts each chair stand and records stand if less than 5

- Records and explains unusual values
- Starts timing with “Go”, stops with final stand or one minute
- If task was not performed, codes and explains reasons

Standing balance

Side-by-side stand

- Script correctly and clearly delivered
- Correctly demonstrates position
- Timing started coincident with participant release and stopped when participant takes a step or grabs for support
- Records timed measure within 0.5seconds of QC officer or designated personnel
- If task was not performed, codes/records reasons

Semi-tandem stand

- Script correctly and clearly delivered
- Correctly demonstrates position
- Timing started coincident with participant release and stopped when participant takes a step or grabs for support
- Records timed measure within 0.5seconds of QC officer or designated personnel
- If task was not performed, codes/records reasons

Tandem stand

- Script correctly and clearly delivered
- Correctly demonstrates position
- Timing started coincident with participant release and stopped when participant takes a step or grabs for support
- Records timed measure within 0.5seconds of QC officer or designated personnel
- If task was not performed, codes/records reasons
- Repeat (second trial), if necessary

4-meter walk

- Script correctly and clearly delivered
- Correctly demonstrates
- Toes touching start line
- Timing started coincident with participant’s first movement
- Time stopped when the first foot crosses an imaginary plane extending vertically up from the ending line/tape
- Repeat (second trial)
- Records timed measure within 0.5 seconds of QC officer or designated personnel
- If task was not performed, codes/records reasons

13.2 Equipment Checks

Every six months: Check the calibration of the grip strength dynamometer by hanging 5 kg and 20 kg (or 10 and 50 lb.) weights across the handle using two Velcro straps, one strap on each side of the dynamometer handle, or one wide strap that covers the whole handle. Lift the weights slowly from the floor while they are strapped to the dynamometer handle and record the maximum kilograms registered. The lifting motion should be very slow and smooth, and the weight should remain evenly distributed between the two sides of the handle. Repeat the procedure three times and record each result. Average the three calibration trials. The dynamometer should be accurate within ± 2 kgs for the average of the three calibration trials. It may be necessary to send the dynamometer to the manufacturer for repair and recalibration. DO NOT attempt to recalibrate the dynamometer yourself. Calibration problems can be caused by dropping the dynamometer or by leaks in the hydraulic system.

13.3 Training and Certification for Grip Strength Assessment

Examiners are centrally trained prior to the start of the study. Study coordinators are responsible for training new staff if necessary after central training based on standardized QxQ instructions.

The examiner requires no special qualifications or experience to perform this assessment. Training will include:

- Read and study the manual
- Attend ARIC training session on performance test administration techniques (or observe administration by experienced examiner)
- Practice on other staff or volunteers
- Discuss problems and questions with local expert or QC officer
- QC officer or designated person may review video of 2 performances if necessary

Certification will include:

- Complete training requirements
- Recite exclusions
- Conduct exam on two volunteers:
  - According to protocol, as demonstrated by completed QC checklist
  - Results agree within $\pm$ 2 kilograms of QC officer for grip strength

QC elements required for certification are:

- Participant is asked about recent surgery on hands
- Participant is asked about pain and arthritis in hands
- Recording dial reset to zero after sub maximal practice and each trial
- Appropriate hand placement and grip adjustment if needed
- Appropriate position of participant and dynamometer
- Reviews and correctly completes form

13.4 Training and Certification for the Two Minute Walk (TMW)

Examiners are centrally trained prior to the start of the study. Study coordinators are responsible for training new staff if necessary after central training based on standardized QxQ instructions.

The examiner requires no special qualifications or experience to perform this assessment. Training will include:

- Read and study the manual
- Attend ARIC training session on performance test administration techniques (or observe administration by experienced examiner)
- Practice on other staff or volunteers
- Discuss problems and questions with local expert or QC officer
- QC officer or designated person may review video of 2 performances if necessary

Certification will include:

- Complete training requirements
- Recite exclusions
- Conduct exam on two volunteers:
  - According to protocol, as demonstrated by completed QC checklist
  - Distances recorded are within $\pm$ 1 foot of QC officer measurement

13.5 Quality Assurance/Certification Checklist for the TMW

Preparation

- Checks blood pressure and heart rate using vitals previously taken
- Reviews exclusion criteria:
  - Used walking aid for 4-m walk
  - SBP $\geq$190 or DBP $\geq$ 110
  - Heart rate >120 bpm
  - Cast or immobilizing device on leg
- Clearly delivers key points from script for each test
- Correctly describes the test
- Correctly demonstrates walking the course (around the cone)
- Explains stop protocol
- Prepares a piece of tape to mark where participant stops

2-Minute Walk

- Instructs participant to walk as quickly as they can
- Encourages participant every lap
- Gives 1-minute warning
- Marks and records number of cones passed
- Offers rest period if needed and encourages resting participant to resume when ready
- Gives participant notice when 1:45 time elapsed and walks to participant at 2 minutes
- Places tape behind participant's heel
- Records whether or not the participant completed the walk and if not, why
- Reviews form for completeness
- Accurately measures and records distance
- Describes appropriate responses to symptomatic participants during TMW

Maintaining proficiency in the administration of the physical function measures requires regular exposure to the protocol. In order to maintain certification, primary examiners will administer the neurocognitive measures at least 4 times per month (Appendix 6). Quarterly, these reviews are

summarized onto the Summary of Observation and Equipment Checklist (Appendix 1), which is then sent to the Coordinating Center

13.6 Quality Control

The data collected by each examiner are periodically reviewed by the Quality Control Committee from quality control analyses performed by the Coordinating Center. Data patterns suggestive of deviations from protocol are brought to the attention of the field center principal investigator and study coordinator. Observation of the assessments then follows, with discussion of possible remedial actions with staff. Major deviations are brought to the attention of the QC Committee.

14. Peripheral Neuropathy

The measures of peripheral neuropathy include a visual assessment for amputations, lesions, and ulcers and monofilament testing.

14.1 Training and Certification

Videos are available online to demonstrate the monofilament test (https://www.youtube.com/watch?v=TFNDs79mQlE or https://www.youtube.com/watch?v=W_9DjStRFww). The videos, ARIC manual, forms, and QxQ should be reviewed prior to the initial training session. Training will include:

- Demonstration of monofilament buckling and the monofilament test
- Proper care of monofilaments
- Practice administering the test, ensuring the monofilament is applied for the proper length of time and the tone of voice is neutral while stating “A, B”

To complete certification, each technician should administer the peripheral neuropathy test on another technician and have two or fewer technician errors.

Technicians should review the manual and the order of monofilament tests periodically, and practice as needed on themselves or other staff.

14.2 Equipment Checks

The instrument (AliMed reusable nylon Semmes-Weinstein Monofilament, 5.07), which was used for the first ~500 participants has been discontinued by the manufacturer and is no longer available. Thus, we will replace this instrument with disposable monofilaments. The impact of the change should be minor and we do not anticipate major challenges for the Field Centers in implementing this change. The only change to the protocol will be that the disposable monofilaments will be used for one participant each and disposed of after each use. Field Centers will be provided a “monogripper”, a plastic handle to hold the new disposable monofilaments. All Field Centers will begin using the new disposible instruments on October 10, 2016.
Please contact Dr. Liz Selvin (eselvin@jhu.edu) so that an adequate supply of monofilaments can be made available to each field center.

14.3 Quality Control

The data collected will be periodically reviewed by the coordinating center. If a technician has a high error rate, defined as >10% of participant exams with >3 “could not be obtained due to technician error” per participant exam, it will be brought to the attention of the field center study coordinator and re-training should be conducted.

15. Zio®XT Patch

The Zio®XT Patch will be applied to identify subclinical or symptomatic atrial fibrillation (AF) and to measure AF burden. In addition, it will be used to record the occurrence of various forms of cardiac arrhythmias.

15.1 Training and Certification

A training video for the Zio®XT Patch is available online and can be found at **https://vimeo.com/channels/irhythmzio**. This video should be reviewed prior to the webinar training (April 28, 2016), initial in-person training session (May 10, 2016), and every 6 months after the initial in-person training session. Staff can be trained centrally or locally.

Training includes:

- Watch the online video
- Study the ZIO form and ZIO form QxQ
- Webinar
- Attend ARIC in-person training session or be trained at the ARIC field center by an experienced staff. During the in-person training session, in addition to hands-on training in applying the Zio®XT Patch, we will review a training slide deck and Zio Patch study checklist

Requirements for certification include:

- Recite exclusions
- Apply the Zio®XT Patch on 1 volunteer
- Be familiar with iRhythm (the Company) secure website
- Be familiar with the ZIO form and QxQ
- Be familiar with contents in training slide deck
- Be familiar with Zio Patch study checklist

15.2 Equipment Checks

Field center staff will need to regularly check the Zio®XT Patch inventory to ensure that the devices are not expired. Devices that will be expiring soon will need to be returned to iRhythm before they expire.

15.3 Quality Control

We will be monitoring the following:

- Performance of the Zio®XT Patch
    - Mean and median wear time
    - Mean and median analyzable time
- False positive findings
    - To avoid false positive findings, EPICARE (Wake Forest University) will download the standard report from the iRhythm website on a daily basis. Under

the direction of Dr. Elsayed Soliman a team of ECG readers will verify the accuracy of arrhythmia diagnoses and clinical relevance of abnormalities in the iRhythm standard report.

- False negative findings
    - Dr. Larisa Tereshchenko (Oregon Health & Science University) will have access to the raw data files. To determine whether AF episodes are missed by the iRhythm algorithm, Dr. Tereshchenko will use custom software to analyze the complete raw data of a sample of participants to establish the sensitivity of the iRhythm algorithm. This further allow investigators to correct for measurement error for statistical evaluation of these data.

16. Audiology

Audiology measures include the Self-Reported Hearing and Noise Exposure (HNE) questionnaire, the Hearing Handicap Inventory for the Elderly – Screening (HHI) questionnaire, otoscopy, pure-tone audiometry (250-8000 Hz), QuickSin speech in noise measurement, and tympanometry (if time permits). The questionnaires will be collected in a quiet room while all other measures will be collected in a sound-treated booth in the clinic. When conducting home-based visits, only the questionnaires and pure-tone audiometry will be collected. These measures will allow for qualitative and quantitative assessment of an individual's hearing loss and how it relates to other areas of cognitive and physical functioning. This section of the manual supplements the Audiometry Manual of Operations by reviewing training and certification, equipment checks, and quality control.

16.1 Training and Certification

The Audiometry Manual of Operations, forms, and QxQs should be reviewed prior to training whenever possible. Training and certification will be broken down into a series of sessions that include centralized training, site based training, and long-distance follow-up.

- Centralized training will include a detailed overview of the two questionnaires, the procedures for otoscopy, and how to recognize difference otoscopic outcomes for the CRF.
- Site Visit #1: A representative from Johns Hopkins will conduct a day training session reviewing questionnaires and otoscopy but focusing on pure-tone audiometry, QuickSin, and tympanometry measures. All technicians will complete a mock run through of the procedures and are encouraged to continue practice between sessions.
- Site Visit #2: A local audiologist will come to the ARIC center and oversee the execution of a mock visit by each technician to be certified. This session will be recorded via GoPro technology (provided by Johns Hopkins) and evaluated by the Johns Hopkins based team for accuracy.
- Certification will be granted based on completion of training sessions, review of all materials, and accurate completion of mock session as determined by two or fewer errors in procedure.
    - Certification will be maintained by completing at least 4 visits per month.
- A refresher one-day on-site training will be conducted by a representative from Johns Hopkins within two months (approximately August 2016) of the start of data collection.

16.2 Equipment Checks

On an annual basis, audiometric equipment will be assessed and calibrated by professional equipment distributors. For most equipment, this will require a technician to visit the ARIC

center while for some equipment, it will require sending the equipment away for calibration. This will be coordinated with local centers by the Johns Hopkins based team.

On a weekly basis, the Interacoustic Equinox 2.0 audiometer and ShoeBox audiometer should undergo a biologic check for accuracy. This procedure involves evaluating one or two technicians' pure-tone audiogram on a weekly basis and comparing their results to their baseline hearing test to ensure the audiometer is still accurate within 10 dB. Essentially, the equipment is being assessed for reliability based on the assumption that a person's pure-tone hearing thresholds should not change week to week. It is possible for a technician to have a natural shift in hearing which is why it is critical to have multiple baselines to compare against. Please see the manual for detailed weekly equipment check procedures.

On a daily basis, all equipment should be checked for regular wear and tear, proper connections, and quick listening checks for functionality. The Titan Middle Ear Analyzer should be calibrated daily using a 2.0cc calibration cavity. In addition, equipment should be plugged in and charged and cleaned using appropriate cleaning wipes (Audio Wipes) between uses. Please see the manual for detailed daily equipment check procedures.

All annual, weekly, and daily equipment maintenance checks should be recorded in a binder. All manuals for equipment will be stored on the desktop computer associated with the audiometer. Please reach out to your local equipment distributor (outlined in manual) or Nicholas Reed at Johns Hopkins (nreed9@jhmi.edu) with any equipment issues.

16.3 Quality Control

For purposes of sustained excellence in data acquisition, a yearly on-site re-training session from a representative from Johns Hopkins will be conducted. During year one, this will be in addition to the approximately two-month follow-up re-training session. In addition, biannual mock sessions by technicians will be recorded via Go Pro technology and reviewed for accuracy.

The data collected will be reviewed periodically by the coordinating center and hearing committee. This will be more frequent early on in data collection including the review of each technician's first ten participants' data. A high number of data outliers (based on comparison to normative data) or unable to obtain data responses (> 5% when compared to the other technicians) will be brought to the attention of the field center study coordinator and re-training will be conducted.

17. Physical Activity and Falls

17.1. Physical Activity via Accelerometry

The measures of physical activity via accelerometry include: 7-consecutive days of accelerometer (i.e., activity monitor) data and an activity monitor tracking log (Form AMT). The activity monitor is the red device worn on the waist via an elastic belt.

17.1.1. Training and Certification for Activity Monitor Assessment

Examiners are centrally trained prior to the start of the study. Study coordinators are responsible for training new staff if necessary after the centralized training based on the standardized QxQ instructions. The examiner requires no special qualifications or experience to perform this assessment. Training will include:

- Read and study the manual and study related materials, including the (1) Physical Activity and Falls Ancillary Study protocol and overview of study processes, (2) overview

of activity monitor data collection, (3) written participant instructions, (4) frequently asked questions about wearing the activity monitor, (5) participant checklist to facilitate activity monitor and activity monitor tracking log (Form AMT) return and (6) participant check-in's and equipment recovery protocol including telephone scripts and reminder postcards.

- Attend centralized training session (or observe administration by experienced examiner) that provides detail on: (1) preparing activity monitors for field data collection, (2) instructing participants on how to properly wear the activity monitors and complete the activity monitor tracking log in the field, (3) data download and file transfer, and (4) activity monitor retrieval protocol.
- Practice on other staff or volunteers.
    - ***Practice-based Experience #1:*** *Practice the process for (1) fully charging the activity monitor device, (2) initializing the activity monitor for data collection, and (3) instructing a volunteer on the proper wear of the activity monitor and completing of the activity monitor tracking log.*
    - ***Practice-based Experience #2:*** *Each examiner should initialize the activity monitor and wear it for 2-3 days. Once 2-3 days of data collection are complete, practice the process for (1) data download and (2) data file transfer (via Secure Software) to the UMMC Biostatistics Group.*
- Discuss problems and questions with Dr. Kelley Gabriel (UTHealth) or QC officer.

<u>Certification will include</u>:

- Complete training requirements.
- Complete practice-based activity #1 and #2 (see above).
- Recite inclusion / exclusion criteria for Physical Activity and Falls Ancillary Study.
- Conduct mock instruction with two volunteers.

<u>QC elements required for certification are:</u>

- *Practice-based activities #1 & #2:*
    - Downloaded activity monitors successfully sent to UMMC Biostatistics Group via Secure Software.

- *Mock Instruction:*
    - Examiner provides overview of accelerometer, including instructions for proper wear.
    - Examiner provides overview of activity monitor tracking log, including instructions for proper completion.
    - Examiner demonstrates proper wear of the activity monitor using the elastic belt.
    - Participant is instructed to place the activity monitor on his/her right waist; adjustments to the elastic belt length are also made at this point.
    - Participant is instructed on how to properly complete the activity monitor tracking log. Including the questions on the back-side of the log that pertain to his/her experiences during the 7 days of wear.
    - Examiner provides an overview of materials that are included in the accelerometer take-home package, including: (1) activity monitor tracking log, (2) written participant instructions, (3) list of frequently asked questions, (4) participant checklist, and (5) pre-paid and addressed padded envelope.
    - Examiner provides instruction on how to return the (1) activity monitor, (2) activity monitor tracking log, and (3) participant checklist in the pre-paid and addressed padded envelope after 7 consecutive days of wear.
    - Examiner indicates that the participant will receive a telephone call 3 and 10 days after the in-person visit.

17.1.2. Equipment Checks for Activity Monitor Assessment

Checked prior to (i.e., day of) in-person exam

- ActiLife software functioning.
- Activity monitor battery charged ≥ 95%.
- Sample rate set to 40 hertz (Hz).
- Flash LED during delay mode / Flash LED during data collection boxes unchecked
- Activity monitor initialized to start data collection at 12am (**Use Atomic Server Time**) the day of the NCS Visit 6 exam visit.
- Stop date and time NOT selected / indicated.
- Participant's unique ARIC Study ID entered as "subject name".
- Activity monitor attached to sanitized elastic belt.

Checked during in-person exam

- Participant places activity monitor over his/her right hip, secured by the elastic belt.
- Accelerometer take home package includes: (1) activity monitor tracking log, (2) written participant instructions, (3) list of frequently asked questions, (4) participant checklist, and (5) pre-paid and addressed padded envelope.
- (1) Participant's unique ARIC Study ID, (2) activity monitor number, (3) date of distribution, and (4) date of expected return (2 weeks following in person visit), and (5) other required details are recorded in the tracking system to facilitate field data collection.

17.1.3 Quality Control

The data collected by each examiner are periodically reviewed by the Quality Control Committee from quality control analyses performed by the Coordinating Center. Data patterns suggestive of deviations from protocol are brought to the attention of the field center principal investigator and study coordinator. Observation of the assessments then follows, with discussion of possible remedial actions with staff. Major deviations are brought to the attention of the Executive Committee.

17.2. Falls

The Falls measures involve face-to-face surveys/questionnaires at Visit 6. These forms completed during the NCS Visit 6 include: (1) Falls Risk Checklist (STEADI); (2) Falls Efficacy Scale (FES); (3) Falls in prior 6 months (FRM). Participants will also complete, and return, a monthly Falls Calendar (FCL) each month for a period of 6 months following Visit 6. If the Falls Calendar is not returned, then ascertainment of Falls data will occur as part of a follow-up telephone call. In the 6th month, they will also mail back the Falls Calendar Feedback (FCE) form, which evaluates the use of the falls calendar.

17.2.1 Training and Certification for Falls Forms and Falls Calendar

Examiners are centrally trained prior to the start of the study. Study coordinators are responsible for training new staff if necessary after the centralized training based on the standardized QxQ instructions. The examiner requires no special qualifications or experience to perform this assessment. Training will include:

- Read and study the manual and study related materials, including the (1) Physical Activity and Falls Ancillary Study protocol and overview of study processes, (2) Falls Risk Checklist (STEADI); (3) Falls Efficacy Scale (FES); (4) Falls in prior 6 months (FRM); (5) Falls Calendar (FCL) including administration instructions; (6) Falls Calendar telephone follow-up (for calendars not returned after 2 months); (7) the Falls Calendar Feedback (FCE); (8) the Falls Reminder Postcards; and (9) Falls Calendar mailback/recovery outlined in the telephone scripts and reminder postcards.

- Attend centralized training session (or observe administration by experienced examiner) that provides detail on: (1) administer, score and give back the FRC form (STEADI) to participants; (2) prepare Falls Calendars with PATID, (3) instruct participants on how to properly track their falls (and not falling) on the calendar; (4) instruct participants on how to return the individual calendar page at the end of each month; and (5) administer the phone Falls Calendar survey to ascertain falls information from participants when the falls calendar(s) are not returned (after 2 months).
- Practice on other staff or volunteers.
    - ***Practice-based Experience #1****:* Practice providing instructions on how to complete the Falls Calendar (FCL), that are provided on the front page of the calendar, and asking the participant to demonstrate how to complete the calendar every day. Also instruct the participant on how to mail the calendar back at each month, including the Falls Calendar Evaluation (FCE) form, which is located on the last page of the calendar pack.
    - ***Practice-based Experience #2****:* Practice tracking your falls on the Falls Calendar for a few days, as well as following instructions on returning the calendar. Hang up the calendar at home and document daily whether or not you fell, and answering the additional questions as if a fall occurred. Become familiar with the process that the participants are being asked to follow.

- Discuss problems and questions with Dr. Lisa Pompeii (UTHealth) or QC Committee

<u>Certification will include</u>:

- Complete training requirements.
- Complete practice-based activity #1 through #4 (see above).
- Recite inclusion / exclusion criteria for Physical Activity and Falls Ancillary Study.
- Conduct mock instruction for two volunteers.

<u>QC elements required for certification are:</u>

- *Practice-based activities #1 through #2:*
    - Administer practice experiences #1-2 successfully

- *Mock Instruction:*
    - Examiner provides overview of the data to be collected pertaining to falls.
    - Examiner verbally administers the FES and FRM surveys.

- Examiner provides participant with the STEADI form with brief instructions. After the participant completes the form, the examiner sums the score, transfer data from STEADI onto the FRC form (or in CDART) and hand the STEADI form back to the participant with feedback about the score.
- For the Falls Calendar, the examiner first checks that the appropriate calendar is being provided to the participant with respect to the "start month". The examiner then documents the participant's PATID on each calendar page.
- Examiner administers instructions about the falls calendar and demonstrates how the falls calendar should be completed.
- Participant then demonstrates back to the examiner how to complete the falls calendar.
- Examiner instructs participant about how to return the falls calendar (by tearing off a page, placing it in one of the envelopes provided). Participants are informed that the envelopes are already addressed and stamped.
- Examiner informs participant that a reminder post card will be sent to them each month. They will then be informed that if they do not return the calendar, that after 2 months they will receive a call from ARIC and will be asked about falling in the prior 2 months.
- Examiner informs participants about the FCE form on the last page of the calendar and instructs them to complete the form and return it at the end of 6 months.

17.2.2. Checks for Falls Calendar

Checked day of in-person exam

- Ensure the correct Falls Calendar start month (first month of the calendar) (e.g., June start month) reflects the month with which the participant has their Visit 6 exam (e.g., June exam).
- Calendar includes all required pages (6 monthly calendars, 1 feedback form, 7 envelopes)

Checked during in-person exam after participant agrees to be in study

- PATID has been written on each page (7 pages) of the Falls Calendar

17.2.3 Quality Control

The data collected by each examiner are periodically reviewed by the Quality Control Committee from quality control analyses performed by the Coordinating Center. Data patterns suggestive of deviations from protocol are brought to the attention of the field center principal investigator and study coordinator. Observation of the assessments then follows, with discussion of possible remedial actions with staff. Major deviations are brought to the attention of the QC Committee.

18. Adverse Events

As NIH-supported research that involves human subjects, the ARIC study protocol includes procedures for identifying, monitoring, and reporting all adverse events (AEs, both serious (SAE) and non-serious (MAE) events), as well as Unanticipated Problems (UPs). Identification

and reporting of UPs and AEs follow a uniform policy based on the FDA/Office for Human Research Protections (OHRP) regulations and guidance for definitions and timeline

18.1 Training and Certification

To be certified, staff must attend central training, be familiar with the Serious Adverse Event (SAE), Minor Adverse Event (MAE), and the Unanticipated Problem (UPR) forms, QxQs and section 19.7 of Manual 2. The Managing and Reporting Adverse Events and Unanticipated Problems exercises should be completed and sent to the CC (Appendix 14). A staff member who attends the central training and passes certification criteria can train and certify other examiners at the field center.

19. ABI/PWV

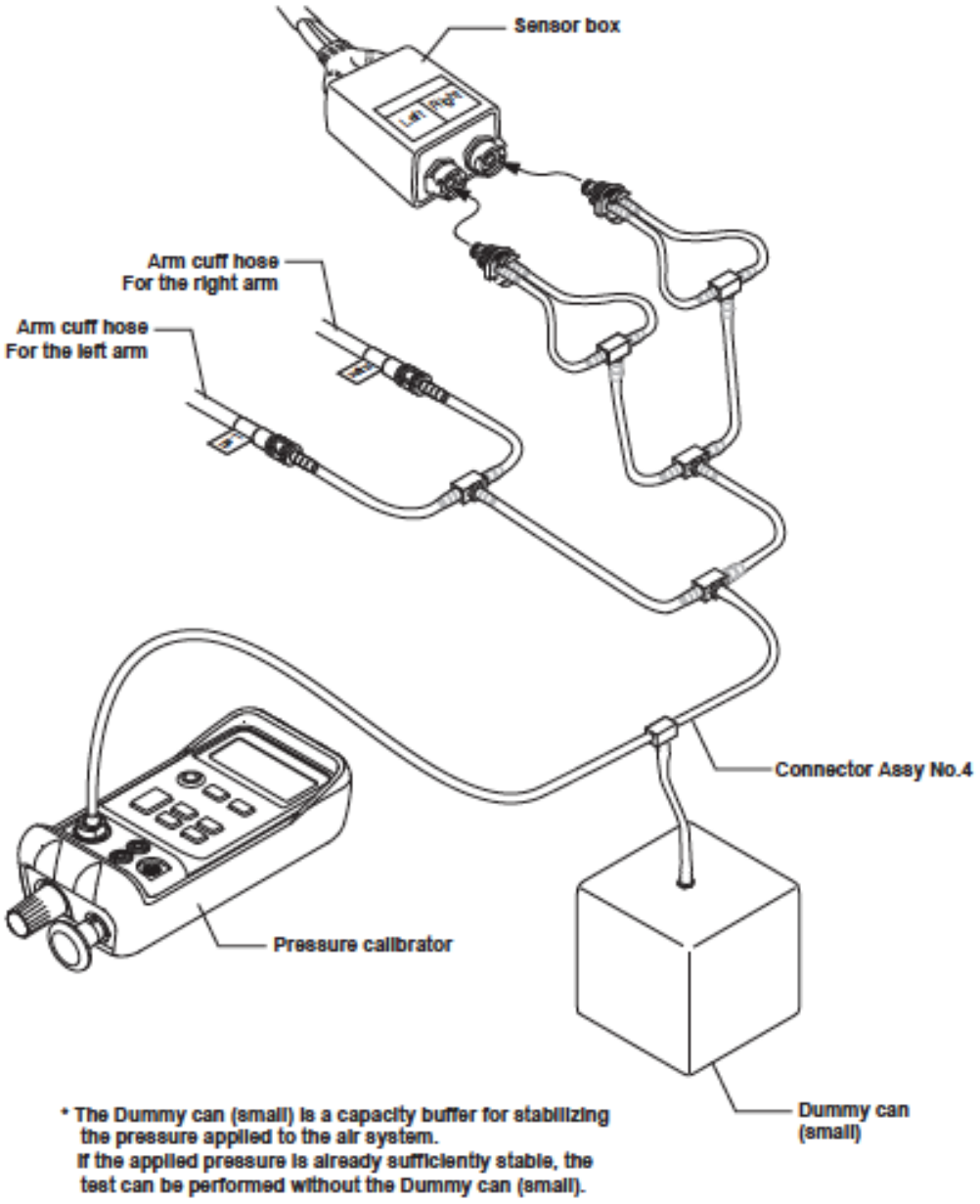
19.1 Equipment Maintenance

A maintenance program is run quarterly (4 times a year) consisting of 1) Air leakage test and 2) Pressure accuracy test. The results are to be recorded on the Pulse Wave Velocity/Ankle Brachial Index Maintenance Sheet (see appendix 15) and submitted to the CC quarterly with the Summary of Observation and Equipment Checklist.

To run the maintenance program, under [Main Menu], choose [Maintenance Menu]. For the Air Leakage test, all the blood pressure cuffs must be wrapped firmly on a 3-inch diameter PVC pipes. Push “Start” to begin the test. The values on the last column (“Diff”) should be 20 mmHg or below after 2 minutes, to pass this test. Air leakage test must be performed on all the blood pressure cuffs used in the ARIC exam. Write down the blood pressure values on the last column (”Diff”) on the maintenance data sheet.

The Pressure accuracy test requires connecting the blood pressure tubing to a pressure calibrator (e.g., Netech DigiMano) through a Y-tube as shown below. Testing will be performed at 3 different pressure settings (50 mmHg, 150 mmHg, and 250 mmHg). Change the inflation pressure to one of the pressure settings and click on “Start Inflation” to begin the test. Ensure that the unit on the Netech DigiMano is “mmHg”. Write down all the pressure values displayed on the Omron machine as well as the pressure reading on the Netech DigiMano on the maintenance data sheet. The pressure values recorded should be within ±3 mmHg of the pressure settings.

It is not necessary to perform the Inflation/Deflation Test.



In general, no maintenance is required on the laptop computer. In case of any system problems, the field center staff contacts the ARIC Coordinating Center.

Appendix 1. Summary of Observation and Equipment Checklists

Instructions: This form should be completed quarterly and sent to the Coordinating Center (CC).

FIELD CENTER ____ DATE: ☐☐/☐☐/☐☐☐☐ (Month / Day / Year)

Quarterly reporting period: Jun-Aug 20☐☐ Sep-Nov 20☐☐ Dec-Feb 20☐☐ Mar-May 20☐☐

A. Observation Checklist

		Technician ID	Supervisor ID	Date (mm/dd/yy)
General interview techniques				
Neurocognitive assessments (review by neurocognitive expert)				
Neurologic Interview (review by neurologic expert)				
Anthropometry				
Sitting blood pressure				
Biospecimen collection				

Physical Function			

B. Equipment Checklist

	Frequency	No. times assessed	No. times within calibration
Anthropometry			
1) Scale read zero	Daily		
2) Weight scales	Weekly		
Blood Pressure			
1) Checks for the OMRON BP machine	Quarterly		
Physical Function			
1) Grip strength dynamometer	Bi-Annually		
Biospecimen collection			
1) Refrigerators, freezers, room temp	Daily		
2) Speed of centrifuge	Annually		
Audiology			
1) All audiometric equipment calibrated	Annually		
2) Interacoustic Equinox 2.0 audiometer checked for accuracy	Weekly		
3) ShoeBox audiometer checked for accuracy	Weekly		
4) Titan Middle Ear Analyzer calibrated	Daily		
ABI/PWV			
1) Maintenance Procedure (submit Maintenance Sheet to CC with this checklist)	Quarterly		

Comments: _____

_____

Appendix 2. Checklist for Observation of Interviewing Technique

ID NUMBER: | | | | | | | |

FORM CODE: | O | I | T |

DATE: 5/3/2016
Version 1.0

ADMINISTRATIVE INFORMATION

0a. Completion Date: ☐☐/☐☐/☐☐☐☐ (Month Day Year)

0b. Supervisor ID: ☐☐☐

0c. Interviewer ID: ☐☐☐

Proficiency in Interview technique	**Yes**	**No**	**Comments**
1. Introduces her/himself at beginning of the interview.	☐	☐	_____
2. Thanks participant at the end of the interview.	☐	☐	_____
3. Explains purpose of interview when appropriate, e.g., reads introductions or transition statements when included on form.	☐	☐	_____
4. States questions exactly as written, stressing time frame and key elements.	☐	☐	_____
5. Demonstrates familiarity with content, flow, definitions, and skip patterns.	☐	☐	_____
6. Uses standardized tone of voice with supportive, non-judgmental statements.	☐	☐	_____
7. Paces interview in response to participant's level of comprehension/comfort.	☐	☐	_____
8. Trains participant in response patterns when appropriate.	☐	☐	_____
9. Refrains from probing except to clarify ambiguous, unclear, or inconsistent responses.	☐	☐	_____
10. Uses standardized definitions when asked for clarification.	☐	☐	_____
11. Repeats questions stressing portions of question which were misunderstood.	☐	☐	_____
12. Interviewer demonstrates knowledge of participant's tracing information.	☐	☐	_____
13. Selects appropriate type of probe.	☐	☐	_____
14. Accurately records participant's responses.	☐	☐	_____

15. Comments: _____

_____

Appendix 3. Checklist for Observation of Anthropometry Measurement

Instructions: This checklist documents observation of anthropometry technicians by supervisors. Quarterly checklists and logs are summarized onto the **Summary of Observation and Equipment Checklists** (Appendix 1).

TECH ID NUMBER: ☐☐☐ SUPERVISOR ID NUMBER: ☐☐☐ DATE: ☐☐/☐☐/☐☐☐☐ (Month / Day / Year)

	Yes	No	Comments
1. Anthropometry is done BEFORE the snack.	____	____	_____
2. If the participant is wearing any nylon hose other than knee highs, the participant is instructed to remove hose.	____	____	_____
3. Participant is wearing light-weight, non-constricting underwear.	____	____	_____
4. Participant is wearing a light clothes or scrub suit.	____	____	_____
5. Participant has removed shoes.	____	____	_____
6. Participant has emptied bladder.	____	____	_____

Weight Measurement	**Yes**	**No**	**Comments**
A. Equipment			
1. Scale firm on floor.	____	____	_____
2. 10 kg standard weight available.	____	____	_____
3. Anthropometry Equipment Calibration log up-to-date.	____	____	_____
B. Procedure			
1. Participant prepared and procedure explained.	____	____	_____
2. Participant is bare-foot.	____	____	_____
3. Position of participant on center of scale.	____	____	_____
4. Balance achieved.	____	____	_____
5. Recordings completed.	____	____	_____

Technician's measurement of participant weight: _____ kg

Supervisor's measurement of participant weight: _____ kg

Waist Measurement	**Yes**	**No**	**Comments**
1. Procedure is explained to participant.	____	____	_____
2. Subject stands erect, yet relaxed, with weight equally distributed on both feet, and feet together.	____	____	_____
3. Place the tape horizontally at the level of the umbilicus (navel).	____	____	_____
4. Subject takes a normal breath and gently exhales, holding breath in a relaxed manner at the end of exhalation.	____	____	_____
5. Tape is horizontal and snug, but not tight enough to compress tissue. [Invert tape, if needed, to insure reading edge of tape is snug to skin for measurement.]	____	____	_____
6. Reading is recorded to the nearest centimeter, rounding down.	____	____	_____

Technician's measurement of participant waist: _____ cm

Supervisor's measurement of participant waist: _____ cm

Comments: _____

_____

_____

Appendix 4. Checklist for Observation of Blood Pressure Measurements

Instructions: This checklist documents observation of technicians certified to perform blood pressure by supervisors. Quarterly checklists and logs are summarized onto the **Summary of Observation and Equipment Checklists** (Appendix 1).

TECH ID NUMBER: ☐☐☐ SUPERVISOR ID NUMBER: ☐☐☐ DATE: ☐☐/☐☐/☐☐☐☐ (Month / Day / Year)

Blood Pressure Measurement	Yes	No	Comments
1. Checks function settings on OMRON unit (ENTER, 3 inflations, 30)	_____	_____	_____
2. Checks Mode and P-setting on OMRON unit	_____	_____	_____
3. Makes sure AC adapter for OMRON unit is securely connected (tends disconnect from unit)	_____	_____	_____
4. Checks AC adapter cord and tubing for cracks	_____	_____	_____
5. Cleans all the equipment	_____	_____	_____
6. Allows subject to rest for five full minutes	_____	_____	_____
7. Performs arm measurement and cuff selection properly	_____	_____	_____
8. Identified brachial pulse location properly	_____	_____	_____
9. Proper cuff placement	_____	_____	_____
10. Attaches cuff to monitor	_____	_____	_____
11. Uses proper settings on OMRON unit	_____	_____	_____
12. Turns monitor on with ON/OFF button	_____	_____	_____
13. Sets MODE selector to AVG	_____	_____	_____
14. Sets P-SET knob to AUTO	_____	_____	_____
15. Pushes START button	_____	_____	_____
16. Records 1st, 2nd, 3rd systolic and diastolic BP readings and average heart rate	_____	_____	_____
17. Instructions to participant are clear	_____	_____	_____
18. Holds arm vertically for 5 seconds between readings	_____	_____	_____
19. Informs participant of average readings	_____	_____	_____

Comments: _____

_____

Appendix 5. Checklist for Observation of Biospecimen Collection and Processing

Instructions: This checklist documents observation of technicians responsible for biospecimen collection processing and shipping by supervisors. Quarterly checklists and logs are summarized onto the **Summary of Observation and Equipment Checklists** (Appendix 1). Copies of this log may be requested by the CC.

TECH ID NUMBER: ☐☐☐ SUPERVISOR ID NUMBER: ☐☐☐ DATE: ☐☐/☐☐/☐☐☐☐
Month Day Year

Biospecimen Collection	**Satisfactory/ Unsatisfactory**	**Comments**
1. Labels checked	___	_____
2. Participant prepared and procedure explained	___	_____
3. Tourniquet application and release	___	_____
4. Venipuncture technique	___	_____
5. Tube collection sequence	___	_____
6. Inversion technique	___	_____
7. Tube incubation location	___	_____
8. Stasis obtained	___	_____
9. Needle disposal	___	_____
10. Laboratory Collection form completion	___	_____

Biospecimen Processing		
1. Knowledge of centrifuge operation	___	_____
2. Aliquotting supply set-up	___	_____
3. Stage 1 tube spin	___	_____
4. Stage 2 aliquotting	___	_____
5. Stage 3 tube spin and processing	___	_____
6. Stage 4 urine and processing	___	_____
7. Volume correct for each aliquot	___	_____
8. Vials sealed	___	_____
9. Biospecimen Form completed	___	_____
10. Freezer organization	___	_____
11. Time constraints	___	_____
12. Disposal of contaminated supplies	___	_____

Biospecimen packing and shipping

1. Specimens bagged ___ _____
2. Adequate dry ice used in shipping ___ _____
3. Shipping paperwork ___ _____

Miscellaneous

1. Incident(s) documented on Biospecimen Form ___ _____
2. QC Procedure ___ _____
3. Containers correctly labeled for shipping ___ _____

Comments: _____

_____

_____

Appendix 6. Checklist for Observation of Physical Function

Instructions: This checklist documents observation of technicians responsible for physical function by the lead supervisor. Quarterly checklists and logs are summarized onto the **Summary of Observation and Equipment Checklists** (Appendix 1). Copies of this log may be requested by the CC.

TECH ID NUMBER: ☐☐☐ SUPERVISOR ID NUMBER: ☐☐☐ DATE: ☐☐/☐☐/☐☐☐☐ (Month / Day / Year)

	Satisfactory/ Unsatisfactory	Comments
Chair Stands		
1. Back of chair against a wall	___	_____
2. Script correctly and clearly delivered	___	_____
3. Correctly demonstrates single stand, emphasizing keeping arms tight across chest	___	_____
4. Correctly demonstrates two stands, emphasizing full stand and return to complete sit	___	_____
5. Says “ready? Go” for each test	___	_____
6. Counts each chair stand and record final time when participant comes to a full standing position on the fifth stand	___	_____
7. Records and explains unusual values	___	_____
8. If task was not performed, codes and explains reasons	___	_____
Standing Balance/Side-by-side Stand		
1. Script correctly and clearly delivered	___	_____
2. Correctly demonstrates position	___	_____
3. Timing started coincident with participant release and stopped when participant takes a step or holds on	___	_____
4. If task was not performed, codes and explains reasons	___	_____
Semi-tandem Stand		
1. Script correctly and clearly delivered	___	_____
2. Correctly demonstrates position	___	_____
3. Timing started coincident with participant release and stopped when participant takes a step or holds on	___	_____

4. If task was not performed, codes and explains reasons ___ _____

Tandem Stand

1. Script correctly and clearly delivered ___ _____
2. Correctly demonstrates position ___ _____
3. Timing started coincident with participant release and stopped when participant takes a step or holds on ___ _____
4. If task was not performed, codes and explains reasons ___ _____
5. Repeats second trial, if necessary ___ _____

Short Walks, *Usual Pace*

1. Script correctly and clearly delivered ___ _____
2. Correctly demonstrates ___ _____
3. Toes touching start line ___ _____
4. Timing started coincident with participant's first movement ___ _____
5. Time stopped when the first foot crosses imaginary plane extending vertically up from the ending line/tape ___ _____
6. Repeats second trial ___ _____

Grip Strength

1. Asked pt about recent surgery on hands ___ _____
2. Asked pt about pain and arthritis in hands ___ _____
3. Recording dial reset to zero after sub maximal practice ___ _____
4. Appropriate hand placement and grip adjustment if needed ___ _____
5. Forearm resting on table, elbow bent to approximate right angle ___ _____
6. Standard encouragement (motivation and feedback) offered to participant ___ _____
7. Recording dial (peak hold needle) reset to zero after first trial ___ _____

Comments: _____

_____

_____

Appendix 7. Anthropometry Equipment Calibration Log

Instructions: This checklist documents the daily, weekly and monthly calibration of anthropometry measurement equipment. Quarterly checklists and logs are summarized onto the **Summary of Observation and Equipment Checklists** (Appendix 1). Copies of this log may be requested by the CC. There should be one such log done each week though the monthly portion will be filled out only in the weeks that it is needed. If there is more than one piece of equipment used for a particular function indicate the checks for each piece on the same log.

Week of:_____ Field Center:_____ Tech ID:____

[Monday's Date]

Daily Checks:

Scales read zero ___ ___ ___ ___ ___ ___ ___

M T W Th F Sa Su

Weekly Checks

A. Reading of scale with 10 kg weight (if reading outside 9.5 to 10.5 range, scale should be serviced.

Date: ___/___/___ Reading: _____

Date service REQUESTED, ____/____/____

Date RECALIBRATED by service technician. ____/____/____

B. Repeat calibration because of moving scales

Date: ____/____/____ Reading: _____

Date: ____/____/____ Reading: _____

Appendix 8. Daily Centrifuge, Freezer, Refrigerator and Room Temperature Log

Tech ID	Date	Centrifuge	Freezer	Refrigerator	Room
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐
______	___/___/___	☐☐☐	☐☐☐	☐☐☐	☐☐☐

1. What does Stage One consist of?

   _____
   _____
   _____
   _____
   _____

2. What pH adjustment is made for the urine samples?

   _____

3. Which centrifuge procedural check points are most critical? (Check all that apply)
   a) Centrifuge temperature _____
   b) Centrifuge speed verification _____
   c) Centrifuge balancing _____
   d) Centrifuge cleaning _____

4. List the tube types to be collected and how many inversions and what temperature each are to be kept.

#	Color/Sample Type	# Inversions	Temperature (RT/Ice)
a) Tube #1	_____	_____	_____
b) Tube #2	_____	_____	_____
c) Tube #3	_____	_____	_____
d) Tube #4	_____	_____	_____
e) Tube #5	_____	_____	_____
f) Tube #6	_____	_____	_____
g) Tube #7	_____	_____	_____
h) Tube #8	_____	_____	_____

5. What is BHT and why is it added to some EDTA plasma aliquots?

   _____
   _____
   _____
   _____

6. Which of the list below are personal barriers that may be used to prevent exposure to biohazardous specimens? Check all that apply
    a) Face Shields _____
    b) Gloves _____
    c) Goggles _____
    d) Lab Coats _____
    e) All of the above _____
    f) None of the above _____

7. List what is included in "Day ONE" preparations.
    _____
    _____
    _____
    _____
    _____

8. A partial biospecimen collection does not have to include which tube? _____

9. Which tube # does not require processing? _____

10. Your protocol requires you to centrifuge your samples at 3000 x g for 10 minutes. If your centrifuge is only capable of spinning at a maximum of 2000 x g, how would you adjust your centrifuge protocol?
    _____
    _____
    _____
    _____

11. The phlebotomist should always recap the needle before discarding for the safety of waste disposal personnel. True_____ False _____

12. The buffy coat is embedded in the red blood cells requiring the removal of all the red cells. True _____ False _____

13. In the home setting, a patient is bed ridden and cannot sit upright. How do you handle the blood draw?
    _____
    _____
    _____
    _____
    _____

14. In shipping, it is okay to label only the secondary bag since all samples have the participant's ARIC ID label affixed. True _____ False _____

15. Since a maximum of 90 minutes is allowed for completion of stages one through three for clinic visits, when do you actually start your timer(s)?

_____
_____
_____
_____
_____

16. List how many aliquots you should have next to the sample type listed below:
    a) SST Serum _____
    b) EDTA Plasma _____
    c) PAXgene sample _____

17. The Quality Control (QC) Phantom collection consists of which tubes and how are they processed?

_____
_____
_____
_____
_____
_____

18. During the blood collection process, when are the QC samples drawn?
    a) Before tube #1 _____
    b) After tube # 8 _____
    c) Between tubes #2 and #7

19. All blood samples must be handled as potential _____.

20. When a participant arrive at the clinic or you arrive at the home site, what checks do you make?

    a) Confirm the match between the participant name and the ARIC ID _____
    b) Confirm that labels match on collection tubes _____
    c) Confirm that labels match on urine specimens _____
    d) Confirm that labels match on aliquot vials & Biospecimen Form _____
    e) Check that duplicate QC tubes are prepared & labeled if needed _____
    f) None of the above _____
    g) All of the above _____

Appendix 10. OMRON BP Monitor Maintenance and Calibration Log

Instructions: This checklist documents the quarterly checks for the OMRON BP machine. There should be one such log done every quarter. If there is more than one BP monitor used indicate the checks with a separate log for each monitor. Quarterly checklists are summarized onto the **Summary of Observation and Equipment Checklists** (Appendix 1).

TECH ID NUMBER: ☐☐☐ FIELD CENTER ☐ DATE: ☐☐/☐☐/☐☐☐☐ (Month / Day / Year)

Blood Pressure Measurement **OMRON unit #:**_____

	Y/N	**If YES, action**
Cracking		
Holes		
Worn outer cloth of Velcro		
Leakage of cuff bladder		
Calibration Check with Pressure-Vacuum Meter		
Smooth descent of OMRON LED mm Hg from 280 to 20 mm Hg		
Observed pressure values 250 to 20 mmHg, in approximant decrements of 20 mmHg	**OMRON (mmHg)**	**Pressure-Vacuum Meter (mmHg)**
Measurement Number 1	☐☐☐☐.☐	☐☐☐☐.☐ mmHg
Measurement Number 2	☐☐☐☐.☐	☐☐☐☐.☐ mmHg
Measurement Number 3	☐☐☐☐.☐	☐☐☐☐.☐ mmHg
Measurement Number 4	☐☐☐☐.☐	☐☐☐☐.☐ mmHg
Measurement Number 5	☐☐☐☐.☐	☐☐☐☐.☐ mmHg
Measurement Number 6	☐☐☐☐.☐	☐☐☐☐.☐ mmHg
Measurement Number 7	☐☐☐☐.☐	☐☐☐☐.☐ mmHg
Measurement Number 8	☐☐☐☐.☐	☐☐☐☐.☐ mmHg
Measurement Number 9	☐☐☐☐.☐	☐☐☐☐.☐ mmHg
Measurement Number 10	☐☐☐☐.☐	☐☐☐☐.☐ mmHg
Measurement Number 11	☐☐☐☐.☐	☐☐☐☐.☐ mmHg
Measurement Number 12	☐☐☐☐.☐	☐☐☐☐.☐ mmHg

Appendix 11. Certification Request Form

Instructions: This form documents which procedures/interviews a staff member is certified for and how they received certification. It is submitted by the **Trainer** or **Study Coordinator** to the Coordinating Center (CC) for final evaluation and assignment of staff code number.

NAME OF TRAINER		FIELD CENTER	

DATE: ☐☐/☐☐/☐☐☐☐ (Month / Day / Year)

Staff name _____ or code number ☐☐☐ (if already assigned)

Specify for which procedure/interviews the staff member has completed certification requirements and describe specific actions that were taken to achieve these steps (including supervisors or certified staff members who observed the process).

Procedure & Interview	Date Certified	*Certification Method (choose all that apply)	CC approval (Y/N)
Neurocognitive Test			
Neurologic Interview			
Diabetes/Peripheral Neuropathy			
Zio®XT Patch			
Anthropometry			
Seated BP			
Physical Function			
Adverse Events			
Medication			

CDART			
Quality Assurance			
Accelerometry			
FALLS			
Hearing			
Biospecimen collection, processing			
Interviewing Techniques			
Recruitment			
Survey Instruments			

* 1 = Attended central training presentation
2 = Certified by central trainer
3 = Direct observation by the local certified lead staff member in specified area
4 = Completed written exam
5 = Completed practice. Specify how many sets of practice were performed, and the differences of the measurements compared to the local trainer's for local certification.
6 = Other (specify)
7 = N/A (not applicable to the staff member)
8 = Attended webinar

Coordinating Center Use Only

Assigned staff code number: _____

Date Received: _____ **Processed by** _____

Appendix 12. Timeline for Observation and Equipment Checks

Daily	Anthropometry scales balanced to read zero (Appendix 7) Temperature check in refrigerators, freezers, etc. (Appendix 8) All audiology equipment should be checked for regular wear and tear, proper connections, and quick listening checks for functionality. The Titan Middle Ear Analyzer should be calibrated daily Monofilament cleaned after each participant
Weekly	Anthropometry scales calibrated or when scaled moved (Appendix 7) Interacoustic Equinox 2.0 audiometer and ShoeBox audiometer should undergo a biologic check for accuracy Check the Zio®XT Patch inventory to ensure devices not expired
Quarterly	Review of neurocognitive interview per interviewer by neurocognitive expert, recorded (2 in the first month of the study followed by 1 recording every other month thereafter until the end of the study) (Appendix 1) Review of neurologic interview per technician by neurologic expert, recorded (2 in the first month of the study followed by 1 recording every other month thereafter until the end of the study) (Appendix 1) Summary of anthropometry technicians recorded (Appendix 1) Summary of anthropometry equipment checks (Appendix 1) Blood pressure technicians observed (Appendix 4), recorded (Appendix 1) OMRON BP equipment checks and calibration (Appendix 10), summarized on (Appendix 1) Biospecimen collection, processing observed (Appendix 5), recorded (Appendix 1) Biospecimen equipment checks summarized, info sent to CC (Appendix 1) Physical function technicians observed (Appendix 6), recorded (Appendix 1)
Bi-Annually	Anthropometry technicians observed study coordinator twice monthly for the first month following certification and then twice per year observed (Appendix 3) Grip strength dynamometer calibrated
Annually	Checking of the actual speed of the centrifuge (Appendix 1) Calibration and professional cleaning of pipettes (Appendix 1) All audiology equipment calibrated

Appendix 13. Minimum Frequency of Procedures and Interviews to Maintain Data Quality

Procedure (and associated forms)	Min. # / Month Primary Technicians	Min. # / Month Designated Back-up Techs
Anthropometry (ANT)	6	2
Blood collection & processing (BIO)	4	4
Seated BP (SBP)	4	2
Physical Function (PFX, TMW)	4	2
Medication Survey (MSR)	4	2
Physical Activity (PAC)	4	2
Physical Ability (PAQ)	4	2
Personal Hx (PHX)	4	2
SF-12 Health Survey (SFE)	4	2
Neurologic Interview (ESS, CDP, CDI, NHX, NPI)	4	2
Peripheral Neuropathy (PNF)	2	2
Audiology(HHI, HNE, AUD)	4	2
Zio®XT Patch (ZIO, ZDX)	4	2
Neurocognitive Test		
CES Depression (CES)	2	1
Mini-Mental State (MME)	4	2
Neurocognitive + Summary (NCS)	4	2

Managing and Reporting Adverse Events & Unanticipated Problems
ARIC_NCS Central Training and Certification, 2016

	Event / Occurrence	Type of Event? (a)	Expected? (b)	Study-Related? (c)
1	W006648 is noted to have blood pressure of 210/136 mmHg. The FC nurse is notified, an ambulance is called and the participant agrees to be transported to the ER. After 6 hrs he is discharged home.			
2	Participant feels unwell soon after arriving at the FC and becomes nauseous and has diarrhea. The nurse examines the ppt., who is calm, well hydrated and does not have signs of a medical emergency. The MD on call is notified, who refers the ppt. to his PCP. A same-day appointment is confirmed with the PCP's office.			
3	The ZioPatch was applied incorrectly on the study participant. The participant agreed to have the monitor removed and re-applied, which required abrading and caused some discomfort.			
4	W006746 - 82 yo male fell while getting up following his snack. He denies discomfort after the fall, indicates having tripped over a stool, and agrees proceeded with the exam.			
5	J009274: 75 yo male felt dizzy on standing up after venipuncture and had to be supported by staff to avoid falling. The field center nurse evaluated the participant, and considered him to be stable. After resting for 10 minutes the ppt. completed the exam visit without further incident.			
6	Participant who had neck surgery for a "pinched nerve" 2 months prior to her Visit 6 appointment completes the full examination. Calls the FC three days later to indicate that the severe pain to the shoulder has returned; the ppt. has made an appointment to see her surgeon.			
7	M047731: 76 yo participant stumbles during the timed walk and falls to the ground. No loss of consciousness is observed. The ppt. needs assistance in getting up from the ground. The FC nurse evaluates the ppt., and after a brief rest the ppt. proceeds with the Visit 6 exam.			
8	F072274: 77 yo male arrives at the FC accompanied by daughter as his driver. During administration of the informed consent the ppt. asks for his daughter to assist him because			

Event / Occurrence		Type of Event? (a)	Expected? (b)	Study-Related? (c)
	of difficulty with some of the information presented. The daughter completes several sections for her father and the Visit 6 exam proceeds without further delays.			
9	J066218 - 75 yo female experienced a brief episode of chest pain during blood draw. The study nurse attends to the participant who is by then free of pain and denies discomfort or other symptoms, and wishes to proceed with the exam. The chest pain recurs one hour later, accompanied by weakness. The FC physician on call cannot be reached and the study PI is not accessible due to travel. An ambulance is called and the ppt. is transported to the ED. Following evaluation at the ED the ppt. is discharged home five hours post admission to the ED.			
10	Participant is a 80 yo male who has T2DM treated with an oral hypoglycemic agent b.i.d. As requested by ARIC staff during scheduling, the ppt. did not take his hypoglycemic medication in the morning of the Visit 6 exam. On arrival at the FC it is noted that the ppt. did not bring his hypoglycemic medication to the FC. He asks to proceed with the Visit 6 exam to be able to take the results to his physician. He completes the Visit 6 exam uneventfully.			
11	On her way to the Visit 6 examination a 78 yo participant trips in the parking area provided by the FC and falls, resulting in painful abrasions to both keens and an elbow. There is no indication of loss of consciousness. She asks for a ride to her doctor's office.			
12	The participant's blood pressure is 186/120 mmHg (average of three sitting BP readings). The participant feels well, mentions being forgetful about his BP medication, and asks to proceed with the exam visit. During the exit interview ARIC staff assists the participant in scheduling an appointment with his PCP in 8 weeks, once the ARIC study results are in hand.			
13	W025118 - 75 yo female with hx of myocardial infarction on 11 January 2017 experienced mild chest pain following chair-stands during her Visit 6 exam on March 19, 2017. The ppt. asked to use her nitroglycerin; chest pain improved but she later complained of headache, dizziness. The FC physician on call was notified and an ambulance was called. At that point the participant complained of weakness and feeling cold. She was transported by ambulance to the ED at 10:45 am and discharged from the ED on 20/March/2017 at 5:30 pm.			
14	F007746 - 56 yo male became light-headed following the venipuncture. Nurse asks participant to lie down, takes blood			

Event / Occurrence		Type of Event? (a)	Expected? (b)	Study-Related? (c)
	pressure, which is 132/84 mmHg. Participant then experienced some transient nausea, asked to re-schedule the exam visit and was provided with transportation (taxi) to return home.			
15	During the medical history interview the participant becomes emotional and relates a history of chronic pain. The participant is comforted by staff. The following day the study nurse checks on the participant by phone and learns that she has had several bouts of incontrollable crying since returning from the Visit 6 exam and feels depressed.			
16	Within minutes of eating her snack the study participant indicates feeling dizzy and restless, and experiences tingling around the mouth. The study nurse quickly attends to the participant and rules out hives, swelling, wheezing or difficulty breathing. The symptoms subside spontaneously after 10 min. The participant confirms having a history of food allergies that is not clearly linked to specific foods. In consultation between the participant, the nurse and the physician on call it is decided to proceed with the exam visit.			
17	The participant is a 74 yo man who has twice rescheduled his Visit 6 exam for unexplained reasons. At the time of the safety screen he reports suffering from heart failure and occasional dizziness which has improved since he received an implantable pacemaker. During the exit interview it becomes apparent that bioimpedence measurements were obtained on this ppt.			
18	Ten days after completing the Visit 6 exam the participant calls the field center to report that after increasing discomfort in the area covered by the ZioPatch she has removed the device. She reports that her skin is inflamed in the area, with itching.			
19	The participant is a pleasant 73 yo woman who reports being in good health and has no safety exclusions. During the several of the Visit 6 interviews the participant is observed to be somewhat disoriented and several times asks for help in answering questions. The interviewer administers the six-item screener, which indicates that reliance on a proxy is recommended. In consultation with the study coordinator it is decided to interrupt the exam and ARIC staff assists the participant in identifying a proxy in order to complete the Visit 6 exam at a later time.			
20	At the time of scheduling the Visit 6 exam the ARIC cohort member reports that he has diabetes and is on insulin. He also takes medications b.i.d. for chronic low back pain. The			

Event / Occurrence		Type of Event? (a)	Expected? (b)	Study-Related? (c)
	participant's insulin schedule requires that he have a snack at 9:00 pm, and he is asked to not consume food or drinks after 10:00 p.m. The appointment is scheduled for 7:45 am but at the time of completing the BIO form at the field center it is determined that the participant has by then fasted 13 hours. The study nurse evaluates the participant and it is decided to proceed with the exam visit.			

(a) SAE, MAE, UP, Neither

(b) Is this type of event foreseen in the Informed Consent or study MOP? Yes, No

(c) Likelihood of relationship to participation in ARIC Visit 6: A: Unrelated (clearly not related); B: Unlikely (doubtful related); C: Possible (may be related); D: Probable (likely related); E: Definite (clearly related).

Appendix 15. Pulse Wave Velocity/Ankle-Brachial Index Maintenance Sheet

Pulse Wave Velocity/Ankle-Brachial Index Maintenance Sheet

ID NUMBER: | | | | | | | |

FORM CODE: | P | W | M |

DATE: 11/29/2016
Version 1.0

A. ADMINISTRATIVE INFORMATION

0a. Completion Date: | | | / | | / | | | | | (Month / Day / Year)

0b. Staff ID: | | | |

Instructions: *This form is completed by the PWV/ABI technician during the maintenance procedure on the PWV/ABI system.*

SECTION A – AIR LEAKAGE TEST

1. Enter the values on the last column ("Diff") values

a.	Small right arm cuff		
b.	Small left arm cuff		
c.	Medium right arm cuff		
d.	Medium left arm cuff		
e.	Large right arm cuff		
f.	Large left arm cuff		
g.	Medium right ankle cuff		
h.	Medium left ankle cuff		
i.	Large right ankle cuff		
j.	Large left ankle cuff		

SECTION B - PRESSURE ACCURACY TEST

2. At 250 mmHg

a.	Netech DigiMano reading (mmHg)			
b.	Right arm (mmHg)			
c.	Left arm (mmHg)			
d.	Right ankle (mmHg)			
e.	Left ankle (mmHg)			

3. At 150 mmHg

a. Netech DigiMano reading (mmHg)..... ☐☐☐
b. Right arm (mmHg)..... ☐☐☐
c. Left arm (mmHg) ..... ☐☐☐
d. Right ankle (mmHg) ..... ☐☐☐
e. Left ankle (mmHg)..... ☐☐☐

4. At 50 mmHg

a. Netech DigiMano reading (mmHg)..... ☐☐☐
b. Right arm (mmHg)..... ☐☐☐
c. Left arm (mmHg) ..... ☐☐☐
d. Right ankle (mmHg) ..... ☐☐☐
e. Left ankle (mmHg)..... ☐☐☐

Appendix 16. Monofilament Cross-Over (Instrument Comparison) and Inter-rater Reliability Study Protocol - ARIC Visit 6

Overview: A change was made to the peripheral neuropathy protocol during the early part of ARIC Visit 6 because the original monofilament instrument being used to assess peripheral neuropathy in this protocol (AliMed reusable nylon Semmes-Weinstein Monofilament, 5.07) was discontinued by the manufacturer. Thus, on October 10th, 2016 all field centers switched over to new disposable monofilaments (Medical Monofilaments used with a permanent "monogripper" handle). The only changes in protocol were the elimination of the need for any cleaning with alcohol wipes and rotating/tracking of the monofilament instrument as the disposable instruments are disposed of after each use. The objective of this cross-over study is to evaluate the comparability of the two monofilament instruments (AliMed resusable instrument vs. disposable Medical Monofilament). We will also assess inter-rater reliability of the monofilament testing using the disposable instrument (current protocol). The proposed study will focus on the continuous comparisons of the instruments and is designed to detect large differences.

Study Design: Each field center will identify 20 participants (not necessarily consecutive) to be part of this cross-over study. For these 20 participants at each Field Center (80 participants total), the current Peripheral Neuropathy Form (PNF) protocol will be conducted three times. First, the regular technician will complete the current PNF protocol with the disposable monofilament. Next, a designated technician (one per field center for this study) will conduct the monofilament testing twice, once with the disposable monofilament and once with the reusable monofilament. The order of the monofilament will be randomly assigned (see below): half of the participants will receive the disposable monofilament first, followed by the reusable monofilament, and half will receive the reusable monofilament first, followed by the disposable monofilament. Thus, the study will have the following sequence:

1) First assessment with regular technician according to current PNF protocol (disposable monofilament)

2) Second assessment with designated technician (disposable or reusable instrument – randomly assigned)

3) Third assessment with designated technician (disposable or reusable instrument – randomly assigned)

It will be most efficient and convenient for the participant to have the second and third assessments conducted immediately following the first (standard) monofilament assessment. However, this approach may pose scheduling challenges for the technicians. To address potential scheduling difficulties related to having a designated technician, it is possible that some Field Centers will find it less disruptive to conduct the second and third assessments NOT immediately following the first (standard) assessment. In this scenario, it is acceptable for the technicians to invite a participant who is on break or has completed his/her examinations for the repeat session of the monofilament testing. Please note that this non-concurrent approach to testing will require additional time to remove and replace shoes, socks/stockings etc for a second time.

Data collection: The first assessment represents no change in protocol; the record is collected on the (PNF) Peripheral Neuropathy Form in the V6 Diabetes event. There will be two additional PNF forms completed by the designated technician. The added forms are located in the PNF-QC event. The disposable filament record is recorded on the (PNFD) PNF-Disposable form and the reusable filament record on the (PNFR) PNF-Reusable form. Please note, the calculated fields (items 13,14) do not need to be run for the PNFD and PNDR. The sequence for which monofilament to use first is shown in the table.

Order of monofilament for the designated technician

Participant	1st monofilament	2nd monofilament
1	disposable	reusable
2	reusable	disposable
3	disposable	reusable
4	disposable	reusable
5	disposable	reusable
6	reusable	disposable
7	disposable	reusable
8	disposable	reusable
9	reusable	disposable
10	reusable	disposable
11	reusable	disposable
12	reusable	disposable
13	disposable	reusable
14	disposable	reusable
15	reusable	disposable
16	reusable	disposable
17	disposable	reusable
18	reusable	disposable
19	disposable	reusable
20	reusable	disposable

Data Analysis: To evaluate the comparability of the two monofilaments, we will use the continuous scores (0-24 correct/wrong tests) from the designated technician for each monofilament. We will calculate the Pearson's and Spearman's correlations and visually examine scatterplots and Bland-Altman plots. We will fit a regression line to evaluate if there are any systematic differences between the two measurements by seeing if the intercept is different than 0 or if the slope is different than 1. We will compare the scores with a paired means test, and

assuming a standard deviation of 7 and correlation of 0.7 for 20 participants, we will have 80% power to detect a mean difference of 3.5 points. If the standard deviation is 5, we will have 80% power to detect a mean difference of 2.5 points. If the standard deviation is 7 and the correlation is 0.5 or 0.9, we will have 80% power to detect a mean difference of 4.6 and 2.0 points, respectively. Thus, we will likely be able to detect moderate to large differences between the two monofilaments.

We will also examine the categorical scores for number of foot sites that has decreased sensation (0-8), and the overall classification of the person's sensation (normal, decreased on one foot, deceased on both feet). For these categorical scores, we will use the kappa statistic and the intra-class correlation coefficient (1,1), although these statistics will have minimal power to detect small to moderate differences.

To evaluate the inter-rater reliability, we will use the same analysis plan as for the comparability of the two monofilaments.