Manual 2
Home and Field Center Procedures
ARIC Visit 9 Examination

Version 1.3 – 9/8/2021

Visit 9 Examination
Home and Field Center Procedures
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1 Overview

This manual of operations on Home and Field Center Procedures is one of a series of manuals of operation for the re-examination of the Atherosclerosis Risk in Communities (ARIC) cohort (ARIC Visits). The study is sponsored by the National Heart, Lung, and Blood Institute, NIH.

The study procedures for this examination of the ARIC are set out in separate manuals of operation. Manual 1 provides an overview of the background, aims, organization, and general objectives of the cohort re-examination. Manual 2 refers to the recruitment and re-examination of the ARIC cohort. It details the interviews and clinical measurements conducted as part of the ARIC visit field center and home examinations, cross-referencing the procedures set out in other ARIC visit protocol manuals and those conducted by studies ancillary to ARIC. The procedures and interviews are presented below approximately in the order in which they occur, and in alphabetical order within blocks of interviews. Appendix 1 includes recruitment materials related to the visit, including recruitment letters and scripts. Appendix 2 lists the main components of the home and field center examinations, with reference to their respective study forms.

As all previous examinations of the ARIC cohort, the visit is conducted following strictly standardized protocols of the interviews and examination procedures across all field sites and throughout the duration of the study, in order to optimize data quality. Accordingly, all ARIC field center personnel must be fully familiar with this manual of procedures, be trained and certified in the procedures as described in this manual, and remain standardized throughout the data collection phase. Procedures related to certification tracking and persons responsible for reporting certifications to the CC are described in section 21.2. Mastery of the procedures described in this manual is required so that patterns in the ARIC data can reflect differences between study participants and their characteristics as opposed to differences between study technicians or study center.

This manual mainly covers Visit 9, but also introduces some concepts of future visits; especially Visit 10. Because bio-specimen collection is scheduled for Visits 9 and 11, but is not scheduled for Visits 8 and 10, references to bio-specimen collection remain in this manual, but are not relevant to visits 8 and 10. In some instances, the biospecimen collection topic is shaded with a gray background, in other instances there has been language added to this effect: “If a blood draw is not part of the visit…” or “If a blood draw is part of the visit…”.

To the degree that this is applicable, the description of each interview/exam component in this manual includes a brief rationale for its use, operational procedures, a reference to training requirements and certification criteria, and mention of the quality assurance measures.

2 List of Abbreviations

AFU	Annual follow-up
ARIC	Atherosclerosis Risk in Communities Study
BP	Blood pressure
CC	Coordinating Center
CDART	Carolina Data Acquisition and Reporting Tool
CDR	Clinical Dementia Rating Scale
CES-D	Center for Epidemiologic Studies Depression Scale
CIU	Contact Information Update form
DBP	Diastolic blood pressure
DMS	Data management system
EPICARE	Epidemiological Cardiology Research Ctr (ECG Reading Center at Wake Forest)
ER	Emergency room
ICT	Informed Consent Tracking form
IRB	Institutional Review Board
LTCF	Long term care facility
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
MSR	Medication Survey form
MTC	Medical Therapeutic Classification
NCS	Neurocognitive Study
NDC	National Drug Code
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIH	National Institutes of Health
NPI	Neuropsychiatric Inventory
OHRP	Office for Human Research Protections
PET	Positron-emission tomography
PSA	Participant Safety Screening form
PYP	Pyrophosphate
QCC	Quality Control Committee
QxQ	Question by question
RTS	Recruitment Tracking and Scheduling form
sAFU	Semi-annual follow-up
SBP	Systolic Blood Pressure form
UBACC	University of California, San Diego Brief Assessment of Capacity to Consent
UDS	Uniform Data Set
UPC	Universal Product Code

3 Recruitment to the ARIC Visit

3.1 OVERVIEW

All surviving and willing members of the ARIC cohort are invited to participate in the ARIC visit. Contact and recruitment for the visit can occur as part of the twice-yearly follow-up phone calls to ARIC participants, or on individualized schedules ARIC field center may set up with input from the ARIC Recruitment Committee. Up to 7 phone calls are placed to each cohort member in an attempt to reach all living cohort members and invite them to the exam site or if necessary to have home exams. ARIC staff in charge of recruitment determine whether the participant will attend the field center or will require a home or long-term care facility (LTCF) visit. At the same time, it is determined whether the participant needs to be accompanied to the visit by a proxy (either in the clinic or at home/LTCF). Field centers offer reimbursement for participation expenses, including taxi as needed. When contacting participants for the ARIC visit, staff at each field center can also recruit participants for the Brain Imaging study and schedule appointments for MRI and PET scans. Additional information about recruitment for the Brain Imaging study is provided in MRI and PET Manual 34.

3.2 RECRUITMENT OF PROXIES AND INFORMANTS

As has been done previously, study personnel are likely to interact and consult with individuals who serve as proxies for an ARIC cohort member or as informants who contribute information additional to that provided by an ARIC participant. This may happen at several levels, such as during semi-annual follow-up interviews, recruitment, the informed consent process, or in sharing information on an ARIC participant's day-to-day activities as part of the participant's assessment.

This section provides study-wide definitions for these roles when exercised on behalf of the ARIC participants, general guidance on the criteria by which the need to engage a proxy or informant is determined, and describes their role in recruitment.

An exam proxy is a person who can provide informed consent on behalf of an ARIC participant who is unable to do so for him/herself (for example, if cognitively impaired). The designation of an exam proxy is a process regulated by ethical conduct of research guidelines and is addressed in greater detail in the section on informed consent.

A proxy respondent is a person designated by the ARIC participant who is authorized to provide medical information about the participant to ARIC personnel, and/or sign the Medical Release Form to obtain hospital or physician records for the ARIC study. An exam proxy can be also considered the proxy respondent for follow-up contact.

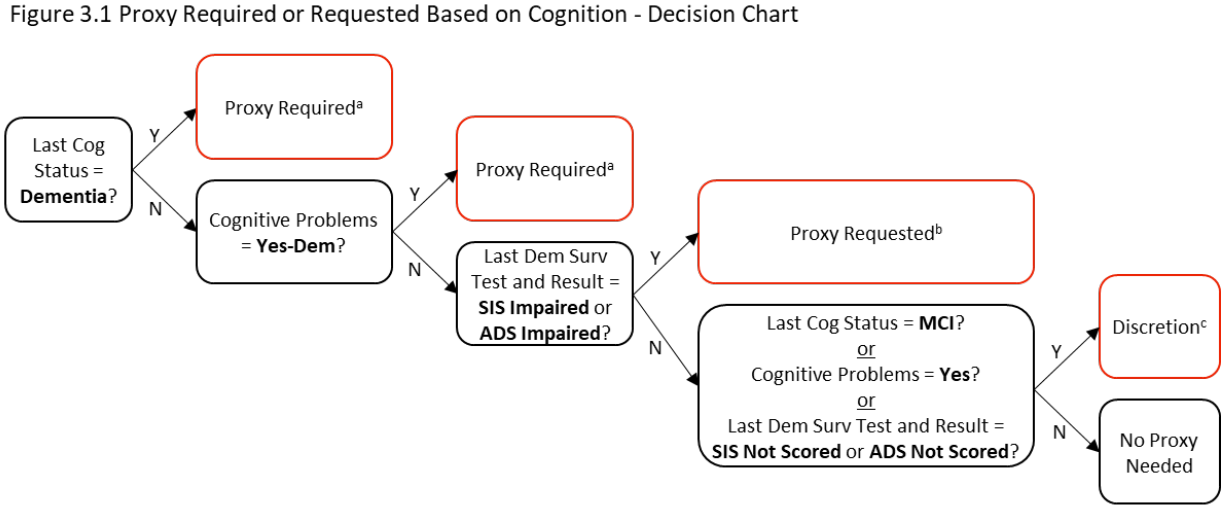
An informant is a person designated by the ARIC participant who is sufficiently familiar with the participant's daily activities to be able to provide adequate information on the behaviors and the functional ability of an ARIC participant. If sufficiently familiar with the participant's performance in the course of daily activities, an exam proxy may serve as an informant. Thus, for most participants, the exam proxy and the informant are the same person, although this is not required.

If at the time of the ARIC visit recruitment call the interviewer perceives that the study participant is being challenged by the interview, possibly confused, or that she/he may experience

difficulties in completing a visit, a decision can be made to request the presence of a proxy at the time of the exam (home/LTCF or clinic). This decision can be aided by administering the Six Item Screener at the time of recruitment. This is an optional screener.

The identification of an exam proxy and informant occurs at the time of the recruitment of the participant. In some cases, the contact person for an ARIC cohort member is already designated as a proxy, so that recruitment and scheduling should be discussed directly with him/ her. If recruitment staff considers that a proxy or informant is needed (see Figure 3.1 and Table 3.1) the participant is asked to identify a person who is close to them and who they trust, so that ARIC staff may contact them in order to facilitate the examination visit. A decision is reached between the recruiter and the ARIC participant on who should contact the proxy/informant. If authorized by the study participant, ARIC staff can contact the proxy or informant, prior to which the ARIC informational and recruitment materials are mailed to them. A phone script for the recruitment of proxy or informants is presented in Appendix 1.

Figure 3.1. Proxy Required or Requested Based on Cognition – Decision Chart



[a] Proxy is required for the visit if the participant has dementia
[b] Proxy is not required, but may be helpful to the participant at the visit
[c] Interviewers use discretion for requesting a proxy/informant based on information in the cognition columns in the Recruitment Report or their knowledge of the participant

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Table 3.1. Is a proxy or informant necessary for this participant's visit exam? – Overview of recommendation per study protocol using the information in the Visit Recruitment Report in CDART . The Recruitment report information below is listed in the order of importance in consideration of the column order in the report in CDART.

Recruitment Report Information	Report Value	Need for a Proxy for Visit?
Last Cog Status based on cognitive diagnosis at previous visit	**D=Dementia[1]**	Required
	M=MCI[4]	Discretion‡
	N=Normal or U=Unknown	No
Cognitive Problems	**Yes - Dem[2]**	Required
	Yes[4]	Discretion‡
	No	No
Last Dementia Surveillance Test and Result	**SIS Impaired or ADS Impaired[3]**	Requested
	SIS Not Scored or ADS Not Scored or None	Discretion‡
	SIS Normal or ADS Normal	No
Last Hearing Loss	Yes	Discretion‡
	No	No

‡ Discretion = The need for a proxy or informant for the visit is based on the interviewer's assessment of the information available, including the result from the Six Item Screener in the RTS form, and/or knowledge of the participant

1 – We have the most confidence in this assessment. This variable will ONLY have a value if the ppt had neurocognitive testing at a previous visit (in-person).

2 – In the absence of Last Cog Status, if the participant had a prior dementia diagnosis, the value of Cognitive Problems will be "Yes-Dem". A proxy/informant is required for these participants as well.

3 – If Cognitive Problems is either 'Yes' or 'No', you must consider the value of "Last Dementia Surveillance Test and Result". If that value shows impaired for either SIS or ADS, then a proxy/informant is requested. Requested means that ARIC personnel can exercise some latitude, based on knowledge of the participant.

4 – There may be some indication of cognitive impairment. The technician should use their discretion in deciding if a proxy or informant should be invited.

3.3 RECRUITMENT OF THE EXAM PROXY

If recruitment of a proxy is necessary at the time of recruitment for the Visit or a scheduling call, the following script can be used:

> "We think that it would be helpful to have someone [come with you to the clinic/be with you while we complete your ARIC examination visit]. This person could assist you in making decisions about participation in the study. Do you agree to have someone [coming with you to the clinic/being with you during the exam]?"

<u>If YES:</u>

> "This person should be someone who can provide consent for your participation in case you do not feel comfortable providing this consent without additional advice. Who would this person be?"

Record the name, street address, phone number and email address if available, and continue:

> "We ask you to tell [PROXY'S NAME] about your decision. In the next few days we will also contact [HIM/HER] to provide information about the exam."

Record the proxy's contact information in the CIU form. Confirm that the participant agrees to communicate with the proxy to request his/her engagement to assist the continued participation in ARIC of the study participant. The proxy is then contacted by ARIC staff a few days afterwards.

If NO:

Point out that having a trusted someone would help to make decisions about participation in the study. If the participant still does not agree, consult the supervisor or Principal Investigator.

3.4 LINKING THE ARIC FOLLOW-UP CALLS AND THE ARIC EXAMINATION VISIT

In earlier ARIC exam visits recruitment occurred at the time of the annual ARIC follow-up phone call. More recently, some field centers have disassociated recruitment of participants from the follow-up phone calls and instead conducted recruitment in a more traditional manner, moving through the list of participants in a way that allows for accommodation of high risk cohort members, snow birds, and/or different schedules for home and LTCF visits. The goal is to avoid approaches that may lead to possible bias in the data collected, allowing sufficient time to recruit all members of the surviving cohort.

To be sure that study participants are made aware of the exam early in the process and can schedule the visit at their convenience, all participants will be invited to the exam during the first 6 months of the visit period in conjunction with the corresponding AFU or sAFU call. However, recruitment coordinators and staff at the field centers can exercise discretion to invite earlier or later some participants, or to separate the recruitment call from the AFU or sAFU calls.

To facilitate recruitment, the Coordinating Center (CC) has created recruitment tools and reports in CDART that include information on all living participants who are still eligible for recruitment. Specifically, the report excludes those who have already been scheduled, have refused, or are lost to follow-up. The report also includes an indicator for ARIC participants also randomized to ACHIEVE. Note that the overlapping ACHIEVE and ARIC participants are less than 7% of the eligible ARIC cohort. The ACHIEVE schedulers will communicate with the ARIC schedulers to enable scheduling for the visit components not collected in ACHIEVE. Those non-shared components are:

Two Minute Walk (TMW)

Alcohol Use questionnaire (ALC)

Medication Survey (MSR)

Continuous Glucose Monitoring (CGM)

These non-shared components can be collected at a number of clinic visit opportunities, but the preferred opportunity is at an ACHIEVE Annual Visit. Proximity to the ACHIEVE annual visit is important from an analytical perspective, so collecting these non-shared components at the

ACHIEVE annual visit should be the first priority. Alternatives for scheduling collection of the non-shared components include ACHIEVE semi-annual visits or an imaging visit. Those shared participants will stay on their ACHIEVE visit schedule. Every effort should be made to coordinate with ACHIEVE staff in order to collect the non-shared data on the participants.

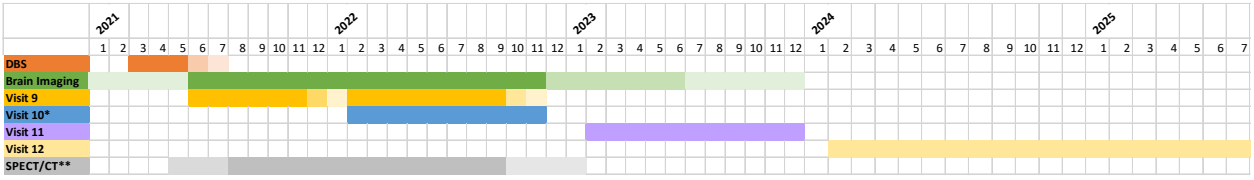
The Visit Exam Checklist for ACHIEVE participants is located in Appendix 2 of this manual.

3.5 RECRUITMENT OF SPOUSAL PAIRS

For efficiency and to make the exam more convenient to participants, field centers try to recruit spousal pairs at the same time, and to schedule their exams on the same day. The visit recruitment report includes information on spousal pairs, which can be used to facilitate recruitment of couples. Field centers should consult their own records to confirm that intact spouse pairs are recruited simultaneously. Spouse pairs where both partners are randomized to ACHIEVE will have shared components collected at the ACHIEVE annual visits. The additional non-shared ARIC components can be collected at ACHIEVE visits (annual or semi-annual) or imaging visits. Recruitment of spouse pairs where one of the partners is randomized to ACHIEVE should be coordinated with the ACHIEVE schedulers to facilitate same-day scheduling. Lists will be provided to the field centers that identify any ACHIEVE-related spouse pair.

3.6 TIME WINDOW FOR ARIC VISITS

In order to accommodate four ARIC visits over a period of 4 years, the exam cycle will range from 10 months to 13 months (depending on the complexity of the visit) with a break between exam cycles to allow for close-out of databases and training for new exam components. Details of start and stop dates will be provided over time, as the timelines may change Currently, Visit 9 and Visit 10 are planned to overlap in 2022, with participants completing Visit 9 first during the time window. Participants are not eligible for Visit 10 until after completing Visit 9; namely the full neurocognitive test battery (Blocks A and B).



The goal will be to schedule visits for each participant approximately one year apart, with the minimum separation of 6 months between visits. Efforts should be made, when possible, to schedule participants for the next visit when they are unable to come in / be scheduled for the current visit. This allows for continuous recruitment into the ARIC visits.

Appointments for MRI and PET scans for the Brain Imaging study should be scheduled a maximum of 6 months before or after a visit. Additional details specific to the Brain Imaging study and ARIC ancillary studies are described in the corresponding manuals.

3.7 SCHEDULING OF VISIT EXAMINATIONS

a. *Overview*

The steps in the scheduling of procedures for the visit are similar to those for scheduling and conducting the ARIC Follow-up Interview, but also include determining whether the participant will require a home/LTCF visit and whether his or her cognitive status requires a proxy for informed consent procedures.

At the discretion of each field center, a letter is mailed to the participant indicating that the usual AFU telephone call will take place, and at that time an appointment for the ARIC visit examination will be set. A brief description of the visit is provided in the letter, as well as a request to have a calendar available to facilitate scheduling. A letter template is provided in Appendix 1.A.

The cohort member is contacted by telephone either at the time of the ARIC follow-up call or independent of the follow-up call. If it is linked to the follow-up call, at the conclusion of the interview the participant is reminded of the new ARIC visit, asked whether the recruitment materials were reviewed, questions are answered, and the cohort member is invited to participate. If possible, an appointment for the visit at the exam site is scheduled.

The participant is asked about any special arrangements for the examination visit, such as medical treatments, transportation, need for assistance in ambulation, or a preference to be accompanied during the exam visit, so that these can be addressed prior to the visit. At the discretion of the field center, these elements are addressed by the recruiter or referred to a designated field center staff person. Information on participant safety and examination logistics identified at this time are recorded on the Participant Itinerary Checklist or the Participant Safety Screener, according to field center practice. These become part of the recruitment record for the participant and are transferred to the field center staff responsible for arranging the exam visit and for the reminder call.

A complete examination at the ARIC field center is the default and is strongly preferred over other options. If the cohort member is unable or unwilling to participate in the complete exam, but is able to come to the exam site, the possibility of conducting an abbreviated exam is offered. If this is not possible, the option of a home visit is offered. Cohort members who are unable to leave their home or are residents of a LTCF are offered the home visit as the first option. Additional details about recruiting participants for the home visit are provided below.

After scheduling the appointment, a reminder letter is sent indicating the appointment time and including the instructions for the exam visit. A document that provides details about the components of the exam as well as its risks and benefits will also be provided. The letter also indicates that a reminder telephone call is made shortly before the examination visit. Contact information for the participant, a proxy, informant or relatives to call the ARIC field center are also provided; questions prior to the appointment are encouraged. The procedures are modified for examinations to be performed at the home or in LTCFs.

b. Pre-Appointment Contacts

As mentioned above, to enhance response following the scheduling telephone call by an ARIC interviewer, a packet is mailed prior to the scheduled appointment. This pre-appointment packet confirms the examination date and time and reviews the preparation procedures. Reminder calls are made to each participant shortly prior to the examination. At this time, the information concerning the collection of all medications and supplements for review at the field center,

adequate clothing and comfortable shoes for the exam, special needs and the use of prescribed medications on the day of the examination are reviewed with the participant. The screening for conditions that exclude a participant from selected examination procedures is also done at this time by completing the Participant Safety Screen form.

c. Contacting Participants

The CC generates from the ARIC database a list of cohort members to be contacted for the visit and their contact month. The list is available in CDART and is called the Recruitment Report. All living participants who have not requested 'no more contact' are included in the CDART Recruitment Report. The Recruitment Report information sheet in CDART has details about how the variables in the report are derived. The CDART list will be available April 2021 for recruiters to use to begin recruiting for Visit 9. It will be important to note the 'months since last visit' (to ensure at least 6 months between visits) as well as the availability of participants given their living and travel situations, especially with only one year to schedule their appointment.

Field centers have the option of mailing a letter to all cohort members informing them about the new exam. A prototype letter is provided in Appendix 1.A. Cohort member address files for producing mailing labels are routinely updated and recorded in CDART. These letters are sent in envelopes stamped "forwarding and address correction requested", to assist in tracking cohort members who have moved.

Approximately one week after the letter is mailed, a telephone call is placed to the cohort member's home. Prior to initiating the joint AFU interview (or visit scheduling telephone call), the interviewer has assembled (1) the AFU form/questionnaire and other relevant forms in CDART, (2) scheduling script, (3) information on reimbursement amounts and transportation, (4) calendar for scheduling field center appointment and home visits, and (5) the Contact Information Update (CIU) form. The recruitment lists prepared by the CC or materials available at the field center identify other ARIC cohort members in the participant's household. If there is more than one ARIC cohort member in a household, the interviewer has the option of completing the AFU and clinic scheduling portions of the interview with each cohort member, or completing the AFU portion with each individual before jointly scheduling their field center appointments (preferred). Prototype scripts are provided in Appendix 1.

Recruitment calls for the visit exam are made as part of the ARIC Follow-up call or the recruitment calls are performed separately. Recruitment calls for the Brain Imaging study can also be performed separately or integrated into the ARIC Follow-up call or visit recruitment call. Each field center keeps track of both AFU completion and visit recruitment status using the RTS form, with tracking provided by the CC in periodic reports to the Steering Committee.

d. Making the Exam Appointment

As the cohort member agrees to participate in the exam visit, the ARIC staff schedules the participant's visit appointment following the prototype script provided in Appendix 1.B. During the first part of the scheduling script the interviewer explains where the clinic is and a decision on whether a clinic or home visit is made and, in the case of clinic visit, whether this is to be a complete or abbreviated exam. Once this has been decided, the interviewer reviews several items to assist in scheduling the appointments:

- Preferred time and date of examination (including morning or afternoon options)

- Establish how participants prefer to get to the ARIC center
- Determine the existence of any medical conditions (e.g., diabetes, dietary restrictions) which might affect the physical examination and/or type of snack provided
- Need for assistance moving around the clinic
- If home visit is required, information on home safety issues and availability of adequate space, and if at a LTCF who to make arrangements with
- How to invite the proxy to be there

The interviewer also mentions that an information packet will be mailed including the specifics of the appointment just made and instructions. Lastly, participants' questions are answered and staff can mention that a reminder call will be made the day before the examination.

If possible, the interviewer schedules appointments for the examination during the 30 days following the telephone call. Field centers, however, can be flexible in scheduling snowbirds or out-of-state residents, to make exams coincide with travel to the field center area. The appointment is recorded on a reminder sheet which is mailed to the participant. Cohort members may be scheduled for appointments at their convenience, including scheduling all eligible members of a single household for examinations on the same day whenever possible. Appointments for MRI and PET scans for the Brain Imaging study can also be scheduled close to the examination date if that is more convenient for the participants.

If a proxy respondent, and not the cohort member, is responsible for scheduling the exam (e.g., if the patient has cognitive impairment or lives in a LTCF), study materials will be mailed to the proxy. If the cohort member is in a LTCF, materials will be mailed to the proxy and LTCF caregivers, but not directly to the cohort member.

After the call, recruiters notify the clinic of participant ID; name, address, and phone number; appointment location (clinic, home, LTCF), time and transportation preference; and any special instructions. Soon after the call, clinic personnel prepare a letter and information packet to be mailed to the participant (see Appendix 1.C. for materials included with this letter). For participants examined in LTCF, in addition to sending study materials to the proxy, a letter notifying the LTCF and asking their permission to conduct the exam will be mailed. Also, if deemed appropriate by the recruitment staff at each field center, a call to the LTCF can be made.

Finally, a reminder call is made on the evening prior to the appointment using "Appointment Reminder Call Script" (Appendices 1.E and 1.F). If the exam takes place in a LTCF, a reminder call will also be made to the facility, though each participant in a LTCF will be approached in a case by case basis (see below for information on home and LTCF visit scheduling).

The outcome of the recruitment call will be recorded in the Recruitment Tracking and Scheduling (RTS) form.

e. Instructions provided to participants after they are scheduled

The instructions for the visit to the field center or the home visits are specified on an information sheet prepared by each field center, and mailed to the participant, proxy, or LTCF caregiver, as

required, soon after the appointment is made. The instructions include (see Appendices 1.C – 1.D) for a letter template including the information below):

- Appointment date and time
- Preparations:
    - Instructions concerning restrictions on the use of tobacco and vigorous physical activity the morning of the visit, and for non-use of perfume, body lotion, baby powder, etc.
    - Instructions on appropriate clothing to wear for the examinations (including comfortable shoes, especially for Zeno Gait Mat and Two Minute Walk)
- Items to bring to the field center or have at the home exam:
    - Eyeglasses for reading
    - Hearing aids, if needed
    - Name and address of primary care physician and/or clinic
    - Name, address, and phone number of contact persons
- Medication Instruction Sheet: Instructions for bringing prescription and over-the-counter medications, including vitamins and mineral supplements, taken within two weeks prior to the examination and a bag for bringing the medications to the field center. As shown in Appendix 1.D, participants are asked to assemble and bring to the ARIC center all prescription, over-the-counter, and research medications, including medications that are solid or non-solid, that may be swallowed, inhaled, applied to the skin or hair, injected, implanted, or placed in the ears, eyes, nose, mouth, or any other part of the body
- Overview of Exam at the Clinic or at home/LTCF (as applicable):
    - A listing of the interviews and procedures for the examination (optional)
    - A reminder that snacks are provided during the exam (both for clinic and home/LTCF exams)
- Clinic hours and phone number for questions or rescheduling appointments
- Directions to the clinic (e.g., a map) and to parking facilities (only for clinic exam):
    - A reminder that free parking or reimbursement is provided
    - Transportation, if applicable (some centers provide transportation and arrange for participant pick-up)

f. Contacts for No-Shows

Eligible participants who fail to arrive for a scheduled appointment or who cancel their appointments are contacted by telephone to reschedule the appointment. At that time, the scheduler tries to address any concerns the participant may have, and address barriers to participation.

Each no-show case is individually reviewed by the interviewer and when necessary by the supervisor. Conversion efforts include a combination of telephone contacts, conversion letters,

and the possibility of offering an abbreviated exam or a home visit. A cohort member is considered to have refused following three conversion contacts or three broken appointments, or if they otherwise firmly refuse.

3.8 HOME/LTCF EXAMINATIONS

As has been done in previous cohort examinations, ARIC will offer the possibility of scheduling home or LTCF visits for cohort members unable or unwilling to participate in the clinic exam. Overall, each field center should aim to have as many participants take part in the clinic exam as possible since the amount and quality of information will be higher during the clinic exam, and the associated costs are lower. However, an examination conducted at home or at an LTCF is preferable to no examination at all.

Deciding whether a participant will undergo home or clinic exam will be done during the initial recruitment/scheduling call. Criteria that should be taken into account when deciding whether a participant needs a home visit are:

- Inability to travel to clinic site due to reduced mobility (because of disability, morbid obesity, or other condition)
- Need to stay at home due to caregiving responsibilities
- Preference: if the only way a cohort member is willing to participate in the exam is with a home visit, the field centers should accommodate this preference

If a home visit is scheduled, the interviewer will collect information on exam proxy need and availability, home safety issues and availability of an adequate setting to conduct the exam (see Appendix 2).

a. Scheduling of Examinations at LTCFs

In most cases, contact with cohort members who reside in an LTCF will not be possible. If this is the case, recruitment and scheduling of the cohort member follow alternate approaches:

1. The recruiter will contact the cohort member's proxy respondent, provide information about the exam, and request authorization for conducting the exam in the LTCF. During this call, the recruiter will obtain contact information for the LTCF and how best to approach the cohort member.
2. Once information on the facility is obtained, an explanatory letter will be sent to the LTCF giving details about the study, the importance of examining the cohort member, and that the member's proxy has provided authorization to conduct the exam in the LTCF. This letter will also mention that an ARIC staff member will phone the facility to schedule an appointment.
3. A few days after the information letter has been sent to the LTCF, recruitment staff will phone the LTCF to request authorization to conduct the exam and, if this is granted, schedule it.

It might be possible to directly contact some cohort members in a LTCF by telephone. In these cases, obtaining authorization from the proxy (step 1 above) will not be necessary. However, once the cohort member agrees to participate, it is recommended to inform and obtain

authorization from the LTCF to conduct the exam (steps 2 and 3). In this case, scheduling will be done talking directly with the participant and, if necessary, involving the LTCF caregivers in this decision.

3.9 RECRUITMENT AND EXAMINATION GOALS BY CENTER

The projected visit exam rates depend on each field center's ability to contact eligible cohort members and schedule appointments. Every effort is made to make the field center or home/LTCF visit as pleasant and burden free as possible. Additionally, the following features are part of the effort to maximize participation: (1) qualified interviewers, (2) pre-appointment contacts, (3) no show procedures, (4) reimbursement of transportation costs, and (5) publicity.

The target recruitment and examination goal for visit 9 will be 50% of living participants. The goals for Visits 10 and 11 will be revisited at a later time. In addition, a cumulative response rate will be tracked, for example, attendance at one of either visit 8 or visit 9, attendance at either visit 9 or visit 10, etc.

a. Reimbursement Policy

Each center provides for, or reimburses, local transportation and/or parking. For those who are reimbursed, records are maintained for accounting purposes according to Office of Management and Budget (OMB) regulations and each university's guidelines.

3.10 MONITORING OF RECRUITMENT PERFORMANCE

Interviewers scheduling examinations report appointment information to their field center daily. Sufficient appointments are scheduled each day from Monday through Friday to meet the recruitment goal.

Each field center maintains the following scheduling documentation:

- A listing of cohort members by ID or name, with telephone number and other contact information (CIU Form)
- Tracking forms for each cohort member (RTS Form). One form per cohort member to track and document the status of each attempt to recruit them to the exam visit.
- Daily appointment log with cohort member's name, ID number, appointment time, and special considerations such as health restrictions. This schedule is used to structure that day's appointments and to check in participants as they arrive.

a. Quality Assurance and Supervision

Throughout the process from initial interview to final examination or refusal, close supervision helps maximize the rate of response. Supervisors record reasons for non-response, and examine performance trends by interviewer and by area. When deemed appropriate, supervisors initiate re-contact with refusing cohort members to attempt their conversion. Detailed records of all contacts are maintained.

3.11 EXAMINATION OF ARIC PARTICIPANTS WHO RELOCATE NEAR ANOTHER ARIC CENTER

Over time, some ARIC cohort members have moved away from the community in which they were recruited and are closer to another field center. These individuals are offered the opportunity to have the new exam at a different field center if this is convenient for them. In essence, however, they remain members of their original field center cohort. Despite data being collected 'off-site' (i.e., at the alternate center), these data are monitored at the original field center, and the original field center is responsible for preparing results reports and letters. The guidelines for implementing these procedures are as follows:

- The original field center continues to perform all Annual Follow-up calls and the scheduling of the field center examinations.
- When cohort members are interested in completing the new clinic exam at another field center, the original field center contacts the closest ARIC field center (i.e., the alternate field center) and arranges for scheduling the appointment.
- The original center sends the ARIC CC and the alternate center written notification of the participant ID, as soon as the participant agrees to complete the exam at the new field center. Notifying the CC is necessary so the alternate field center can access the participant's information through the Data Management System. Scheduling of the clinic exam or home/LTCF visit will be done by the alternate field center after being notified by the original field center. Whether the alternate field center offers travel reimbursement for participating in the clinic exam or the possibility of home/LTCF exam will be decided by the alternate field center, not the original field center. For example, if the study staff has to travel a long distance to reach the participant, the alternate field center could decide not to offer home visit because of costs or time constraints.
- The original field center sends labels and copies of current Annual Follow-up forms and any other pertinent information to the alternate field center. Other pertinent information includes mention of any 'special needs', and copies of prior study results reports and letters to participants and physicians. All this is treated as confidential information.

The Medical Data Review which occurs at the end of the clinic visit is performed by the alternate center. This includes any immediate follow-up to findings during the clinic visit. Subsequent notification of any alert values and the preparation of the report of study results and the accompanying letter(s) to the participant's provider of medical care are the responsibility of the original center.

- Any study data or document collected on paper at the alternate field center will be photocopied, and the originals sent to the original field center. This includes informed consent documents in addition to any other paper forms used during the exam. The alternate center should use any local informed consent forms to gain consent from the participant. The alternate center keeps a copy of all mailed documents until reception of them at the original field center is verified.
- The alternate field center annotates all central agency sample inventory sheets, indicating the special situation. The central agencies (laboratories and reading centers) correspond with the original field center in the event of alert values or other special

issues related to relocated participant data. The original center then sends a copy of the alert to the nurse/clinician at the alternate center for their information, since the participant may call either center with questions. In addition, any local alerts reported through the Data Management System (DMS) at the original field center should be communicated to the alternate field center. In the cases of both reading center and local alerts, the alternate site should contact the participant.

To facilitate coordination between the field centers, contact information for each center is provided in Appendix 1.H.

3.12 TRAINING AND CERTIFICATION OF FOLLOW-UP AND RECRUITMENT PERSONNEL

Interviewers are trained and certified in general interviewing techniques and the administration of the study forms. This requires familiarity with the CDART reports that are available to aid in recruitment (for example, the Recruitment Report, the Recruitment Snapshot, the Annual and Semi-annual Tracing Sheets), assigning contact and appointment status codes on the Recruitment Tracking and Scheduling form, scheduling a field center appointment, and verifying contact information on the CIU form. Recruitment staff is certified centrally by way of Recruitment Committee conference call/webinar

4 Home/Long Term Care Facility Examinations

Home visits provide an opportunity to obtain important data on ARIC participants who are frail, disabled, or cognitively impaired, those who reside in a long term care facility (LTCF), or those who provide dependent care for another person and are unable to come to the field center. At the time of recruitment study participants who meet the above criteria are offered an examination at their place of residence, if they are located within a distance considered to be accessible by the respective ARIC field center. The examination components that are conducted at the participant's home or LTCF are denoted in Appendix 2 – Exam Checklist. Nearly all measurements can be completed in the home. The Physical Function tests (PFX), the Two Minute Walk (TMW) and the Zeno Gait Mat (ZGM) are not completed in home visits or at long term care facility exams. Audiology assessments are performed outside the clinic with the portable audiometer if the environment is suitable.

The interview and physical examination procedures at the home follow the field center protocol as closely as the physical environment permits. Two ARIC staff attend each home visit, one or both of whom are certified in ARIC's protocol for each of the data elements to be acquired.

4.1 ELIGIBILITY FOR A HOME/LTCF EXAMINATION

The ARIC CC periodically provides field centers with lists of cohort members scheduled for recruitment that include several indicators of the possible need for a home visit. Arranging for an examination at a home, nursing home or LTCF may require consultation with the participant's next of kin or proxy, a provider of dependent care, or a nursing facility manager. In the interest of greater comfort for the participant and better quality of study data, cohort members who are frail, disabled, or reside in a LTCF and who are mobile are offered the option of an abbreviated examination at the ARIC field center instead of an examination at their place of residence.

4.2 SCHEDULING AND SETTING UP A HOME EXAMINATION

a. Preparing for the Visit

In scheduling the visit with the participant ARIC staff considers the participant's routines, meal times and rest periods, and attempts to schedule the visit to minimize fatigue. In scheduling a home visit the participant is reminded of the approximate time needed to complete the testing, and the requirement for a quiet and private area with a table and two chairs. ARIC staff carefully explains the need to avoid distractions during the examination period. This applies to interruptions by family members, children, pets, noise from TV, radio, stereo, or phone calls. If there is a pet in the home, the participant is asked whether the pet can be kept in a separate room during the testing (with the exception of service animals used by the participant). In the course of scheduling the examination it is also determined whether the participant's proxy will be available during the home visit. The informed consent process is briefly reviewed with the participant at this time.

The scheduled visit, date, and time are confirmed by letter. The letter includes reference to the physical requirements for home testing, the informed consent video, and the informed consent document (the latter at the discretion of the field center). ARIC staff calls the participant on the day before the scheduled examination, or the morning of the scheduled visit, to confirm the

appointment. If needed, the examination time is adjusted. The participant is reminded of the needed table and chairs, and the need for a quiet space during testing.

ARIC personnel assemble the home examination materials on the day before the home visit. The cognitive testing materials include the bound testing booklet, pencils, stopwatch, and cognitive stimulus materials. The equipment required includes: professional scale (McKesson), the OMRON blood pressure monitor, a laptop computer with an internet connection in order to run CDART, the portable audiometer and a barcode reader. If biospecimen collection is part of the visit, print the participant ID labels and label the biospecimen collection tubes per the Biospecimen Collection Protocol. Prepare the home biospecimen collection kit, biospecimen collection supplies and a small container with ice (for EDTA tubes). Before departing for the home visit, staff verifies that equipment and testing materials are complete, that the directions to the home are clear, and that adequate travel time has been allowed.

b. Staff Safety Considerations

Home visits are made during daylight hours whenever possible. A map and explicit directions are secured before leaving the field center. Travel and home visits are done in pairs. Staff dress conservatively and wear the Study ID in a prominent place. Staff carries a letter of introduction, as well as a copy of the reminder letter or appointment card that the participant should have received earlier.

In the field, staff must remain aware of the surroundings and use common sense for personal safety. A written record of the ARIC visit destination and travel arrangements are left with the home field center, as well as the examiners' cell phone numbers. Purses are locked inside the trunk of the car before leaving (rather than doing this at the participant's home). Staff is encouraged to be cautious of pets, either the participant's or others, and to have car keys in hand when leaving the participant's home (not stand by the car to search for the keys). When directions to the home are obtained, ask whether there are safety concerns or pets (the participant's or others) to be aware of.

c. Liability Issues

At each field center staff seeks counsel on the institutional requirements and the liability insurance policy that covers this work. If paperwork is applicable for purposes of insurance, this is completed before leaving for the home visit.

4.3 CONDUCTING THE HOME VISIT EXAMINATION

a. Establishing Rapport

Appointments are met on time. If a situation arises that prevents staff from being on time, the participant and the contact or proxy if applicable, are called and alerted to the possible delay. Appointments are rescheduled as a last resort. On arrival the examiners introduce themselves and show identification or copy of the appointment letter or card. Appropriate time is spent talking with the participant, family member(s), and/or caregiver to provide a transition from arrival to testing. The content and length of the examination are described, and time is taken to answer any questions that the participant may have.

b. Informed Consent

The informed consent is administered prior to setting up the examination area and proceeding to the examination. This applies to the study participant, the proxy and the informant, if the latter are present per prior arrangement. The informed consent information may be sent one week prior to the home visit, at the discretion of the field center. To administer the informed consent ARIC staff follows the procedures for informed consent administration at the field center described in a following section of the protocol manual.

c. Examination Environment

The environment is assessed for a suitable testing area and if necessary staff refers to the request for the use of a table (kitchen, card, desk, etc.), two straight chairs and adequate lighting. Care is taken to have an exam environment that is as quiet as possible and that pets have been put in a separate room. All persons in the house are made aware that a quiet area and privacy are needed for testing. The participant is asked whether he/she would like to use the bathroom before beginning the testing. If biospecimen collection is part of the visit, it is at this point the urine specimen is collected. A rest period or bathroom break can be offered about midpoint of the testing.

d. Examinations and Interviews

The interviews at the home or LTCF are conducted using the ARIC DMS (CDART) and include the standard versions of the data collection forms used at the field center. The interviews and examinations are administered adhering to the protocol procedures followed at each field center. Similarly, the same quality assurance and quality control protocol applies.

e. Close-out of the Home Examination

After completion of the interviews and examination the participant and proxy or informant are thanked, and asked whether they have questions. Staff mentions that a summary of the results from today's data collection will be mailed in six to eight weeks to the person designated at the time informed consent was obtained. The provisions for continued follow-up calls with the participant or the follow-up interview informant are reviewed, verifying that the respondent is aware of the twice-yearly schedule of the subsequent ARIC follow-up calls. Indications that a different informant or frequency of follow-up calls is desired are recorded and shared with the AFU personnel at the field center. A few minutes are spent in participant-centered conversation as a transition to the departure.

4.4 PROCESSING, TRANSPORTATION, AND SHIPPING OF THE BIOSPECIMENS

The materials and procedures used for biospecimen collection at a home or LTCF are specified in Manual 7. This includes procedures to be followed in transporting these specimens to the ARIC field center, and the prompt processing of the specimens once at the field center.

4.5 ABBREVIATED EXAMINATIONS AT THE ARIC FIELD CENTER

Cohort members who are eligible for an examination at home or long term care facility but are mobile can be offered the option of an abbreviated examination at the ARIC field center instead of an examination at their place of residence. This offers greater comfort to a participant if mobility is not restricted, and a more comfortable as well as standardized environment for the examination. The contents of a 'core examination' conducted at an ARIC field center do not

differ from those conducted at a home (Appendix 2) but field center facilities and equipment are used.

4.6 TRAINING, CERTIFICATION OF PERSONNEL

Collecting measurements and interviews according to a rigorously standardized protocol under the varying conditions of the place of residence of the examinees presents challenges to the ARIC study personnel. Special care and attention to protocol adherence are required to protect the quality of the ARIC data collected under these circumstances. ARIC study personnel who conduct home examinations are trained centrally and are certified prior to being authorized to collect study data. ARIC personnel who conduct home visits is trained in, and certified for the examination procedures and interviews that apply to examinations at the ARIC field centers, and they maintain certification status based on the quality assurance program in place at the field center. Additional training is provided by a supervisor on the implementation of the ARIC procedures in the field, as described above.

4.7 QUALITY ASSURANCE

ARIC personnel who conduct home visits maintain certification status based on the quality assurance program in place at the field center.

5 Field Center Examinations

5.1 OVERVIEW

The ARIC examination is a fully standardized sequence of interviews and procedures conducted according to a common protocol. The components of the visit examination at an ARIC field center are listed in Table 5.1, with reference to the corresponding study forms and the recommended sequence of administration.

Cohort members who are frail or find the ARIC examination too long or demanding may choose an abbreviated version. Such an option is negotiated with the study participant attempting to include as many of the elements set out in Table 5.1 as is possible. Completion of the ARIC core examination (as shown in Table 5.1) takes precedence over measurements conducted by ancillary studies.

5.2 PRIORITY RANKING ASSIGNED TO VISIT DATA ELEMENTS

A priority was assigned by the ARIC Steering Committee for the acquisition of data elements in the visit. Basically, the exam components are listed in priority order Table 5.1. The Exam Checklist, in Appendix 2, is also a template that follows the priority order, but field centers may reorganize the checklists to flow with their clinic set-up and to meet the individual needs of a given participant. The priority order guides negotiations for a shorter examination visit. The order also seeks to include as many of the elements set out in Table 5.1 according to their priority and the study participant's wishes. Completion of the ARIC core examination takes precedence over measurements conducted by ancillary studies.

5.3 MAKING AN APPOINTMENT

Following recruitment, ARIC participants are scheduled for a field center examination or a home visit by the field center recruitment team and/or by personnel at the field center who coordinate this process. Field centers exercise local options to schedule individuals successfully recruited for an examination, and each field center is responsible for entering information promptly into the study screening and recruitment forms so that updated lists used to schedule the field center examination visit can be produced locally.

Before scheduling an appointment, field center personnel must have appropriate scheduling forms and worksheets as used locally, access to the field center appointment calendar of available dates/times, and all relevant scripts. Recruiters make the number of call attempts specified for each ARIC field center, tracking them on the Recruitment Tracking and Scheduling form. If informational materials have been mailed to the study participant prior to the call or left by the recruitment team during household screening, the interviewee is first reminded of the letter and brochure and the staff person reviews this information and answers questions about the study and its procedures, as required.

Table 5.1. ARIC NCS Field Center Examination Components and Estimated Administration Times

Examination Components - Field Center	Forms	Ppt.Time (min)
Reception, informed consent, contact information, safety screen.	ICT, CIU, PSA,	20
Imaging Recruitment		12
Medication Coding	MSR	5
Collection of urine specimen; Blood Draw*	BIO	15
Snack	--	15
Anthropometry	ANT	7
Seated blood pressure	SBP	10
Cognitive Testing: Ensuring speech understanding, Mini Mental Status Exam, CDR with participant, **Block A** (Delayed Word Recall, Digit Symbol Substitution, Incidental Learning, Word Fluency, Animal Naming)[1]	ESU, MME, CDP, NCS	25
Break		5
Cognitive Testing: **Block B** (Logical Memory I, Digit Span Backwards, Trails A & B, Boston Naming, Logical Memory II)	NCS	25
Neurologic history, CES-Depression	NHX, CES	5
Lunch/Snack		20
Accelerometry	ACC	10
Physical function testing, Two minute walk	PFX, TMW	20
Short hearing inventory	HNES	5
Continuous Glucose Monitoring (CGM)	CGM	15
Interviews: alcohol use, physical activity level	ALC,PAC	12
Exit interview (end-of-visit report; review of alerts; accelerometer mailer, CGM mailer)	RAR	10
Cognitive status: informant interview[2]	CDI, NPI	n.a.
Total Time for Visit 9		3 hrs 21 mins
Total Time for Visit 9 with snack, including bathroom breaks and walking time		3 hrs 56 mins

***** Fasting not required

[1]: Participants diagnosed with dementia prior to visit only receive cognitive testing Block A;

[2]: CDI will primarily be collected by phone after the exam based on cognitive testing performance, depending on proxy availability. The CDI is not collected on participants who were diagnosed with dementia prior to the visit.

5.4 PARTICIPANT SAFETY SCREENING

Verification of eligibility for all study procedures and a pre-screening to identify a participant's special needs and to ensure safety are part of the visit scheduling procedures. For this purpose ARIC personnel use the Participant Safety Screening Form (PSA), supported by the ARIC data entry and management system (CDART). Following an explanation of the ARIC study and the procedures involved, the interviewer requests an opportunity to verify the individual's eligibility for all procedures. The rationale for these questions is provided in the instructions for the PSA form, and explained to the participant if requested.

Any medication taken routinely by the participant – on any schedule – is recorded as Yes on item 1 of the PSA form. Only medications that are taken occasionally are recorded as No. The purpose of this question is to prompt ARIC staff to review the medications taken on a schedule with the participant at the time the clinic visit (or home visit) is scheduled. As described below, the participant is then asked to take specific medications on their prescribed schedule, or to defer others until after the blood draw during the exam visit. At the time the participant's visit is scheduled and at Reception after the informed consent is signed, arrangements are made for the participant to have access to medication that needs to be taken in the course of the exam at set times, and with food if required. This is specified on the Participant Exam Checklist (Appendix 2).

The conditions reviewed during this interview (and listed on the form) include the participant's use of a pacemaker, defibrillator or other implanted electronic device, use of an inhaler, and conditions recorded during previous examinations or annual follow-up interviews (diabetes or high blood pressure). Also included in this safety screening are questions about a heart attack, stroke, or surgery during the previous six months. The responses of the safety screening questions are recorded on the PSA form and the participant is told of any procedures to avoid. In preparing for the participant's exam visit exclusions from a procedure are recorded on the Participant Exam Checklist and reviewed with the participant at the time of reception at the field center.

At the time of scheduling the exam staff also inquires about special needs, such as any medical conditions or treatment that would affect the appointment time, difficulties in getting on or off an examination table, or impediments in hearing or reading. Arrangements for a safe and comfortable examination visit are made, inclusive of transportation, consulting with the Study Coordinator as appropriate. Participants should be reminded to bring all their medications to the field center, and the schedule of any medications to be taken on the day of the examination is reviewed (Section 5.5).

5.5 SCHEDULING THE PARTICIPANT'S MEDICATIONS ON THE DAY OF THE EXAMINATION

Participants who have conditions that require the daily use of pharmacologic agents are instructed to do the following on the day of their field center examination:

- Antihypertensive medications should be taken according to the participant's usual schedule for these medications. This is recommended to avoid changes in a participant's usual blood pressure on the day of the examination, and in order to avoid abrupt changes in blood pressure and possible hemodynamic events. Anti-

anginal medication such as Nitrates also should be taken on the day of the examination according to schedule.

- There are no particular safety concerns associated with aspirin, anticoagulants and antiplatelet aggregation agents, although bruising and minimal bleeding may occur at the venipuncture site.
- Medications for cancer, HIV, autoimmune and neurological disorders should be taken as prescribed by the participant's physician. Some of these medications may need to be taken with food, and at set times. Field centers make it possible for the participant to take these medications as prescribed; if this is not practicable the participant is asked to consult with their physician prior to the examination visit.

Key scheduling tasks are:

- explain where the field center is located;
- identify the appointment time;
- establish how the participant prefers to get there;
- identify any special medical conditions;
- provide brief but complete instructions.

The interviewer also mentions that a confirmation letter will be mailed with the specifics of the appointment just made, and a bag for their medications with instructions. Lastly, remaining questions are answered and (optionally) staff can mention that a reminder call will be made. After a successful scheduling call, study personnel process the participant ID; name, address and phone number; appointment time and transportation preference; and any special instructions. The appointments schedule is updated and the "final status" is recorded in CDART.

5.6 APPOINTMENT REMINDERS AND INSTRUCTIONS FOR THE CLINIC EXAMINATIONS

The instructions for the visit to the field center are specified on an information sheet prepared by each field center, and mailed to the participant soon after the appointment is made. This set of instructions is provided in Section 3 of this manual.

5.7 SPLIT FIELD CENTER EXAMINATIONS

The ARIC Visit examination may be scheduled as split exams if the study participant is unable to take part in a full examination, or be split to accommodate circumstances not anticipated at the time the examination was scheduled. Split examinations must be completed no more than 30 days apart. Under exceptional circumstances field center managers may authorize scheduling split examination beyond 30 days. Weather conditions, the unforeseen absence of key ARIC personnel, illnesses, and a participant's inability to complete an examination within the time period specified by protocol represent such exceptional circumstances. The frequency of split examinations that occur more than 30 days apart must not exceed 5% of a field center's examinations during one year.

For visits when blood is drawn, if an exam visit is discontinued after biospecimen was collected, the original venipuncture and specimen processing information is recorded in CDART and not repeated upon return of the participant. Similarly, saliva specimens collected at the time of

urine/blood collection should not be collected again. Blood pressure measurements are repeated (for safety reasons) but the values are not recorded in CDART. The original blood pressure measurements are retained in CDART for reporting purposes. In this scenario, the summary of results report will have the blood pressure from the original visit, and ARIC field center staff should add the updated blood pressure from the repeat visit. The intent is that the lab values and the blood pressure measurements in the ARIC database correspond to the same time point.

5.8 SEQUENCE OF THE FIELD CENTER EXAMINATIONS

Part of the sequence of examination procedures (participant flow) is fixed. Briefly, informed consent must be obtained prior to any data collection, followed closely by the seated blood pressure measurement, as this is an important alert measurement and may result in a stopped visit. Each participant's itinerary can be structured in a way that optimizes participant comfort, data quality, and staff time. Field centers develop participant flow schedules that best fit their staffing pattern and facilities, according to the number of examinees scheduled for the day, adjusted as needed to accommodate cancellations, or unforeseen delays that occur during the participant's progression through the sequence of examinations and interviews. At the field center's discretion, participant itineraries are prepared in advance and printed or displayed for convenient consultation by staff during the examination.

The examination close-out also represents a fixed sequence to assure that a CDART-based data inventory is run to prevent inadvertent omissions in data collection, the on-site report of study results is printed for review with the participant, and instructions are provided for any wearable devices, if applicable.

5.9 PARTICIPANTS SEEN AT A DIFFERENT ARIC FIELD CENTER

Cohort members may be seen at a field center other than their original study site. Communication between the study coordinators at both field centers is essential to accomplish this transfer. The original field center is responsible for maintaining contact and for tracing all study participants who move away from the original study site, with the exception of those who relocate permanently to another ARIC study site.

In the case of a clinic visit to be administered at a visiting field center, the original field center must notify the CC at least two weeks ahead of the scheduled visit. The CC will grant temporary privileges to the visiting field center to access the participant's data in CDART. The ARIC informed consent to be used for this exam visit is that of the (visiting) field center that conducts the exam visit. The visiting field center is responsible for all data entry in CDART for the clinic visit. Reports related to the participant cannot be accessed by the visiting field center and instead must be run by the original field center. This includes, but is not limited to results reports. Exceptions may be made for reports that are run on a specific ID. Report access for the visiting site will be discussed with the CC on a case by case basis.

When the clinic visit and its data entry have been completed, the original study site should contact the CC to request that access to the ID by the visiting site be terminated. The Informed Consent and all materials signed by the participant are to be shipped or mailed to the participant's original center. The chart with paper copies of any materials that do not duplicate what has been entered in CDART is also to be shipped to the participant's original center.

6 Reception

Reception is the first workstation for a participant's examination visit at an ARIC field center. The participant is welcomed, informed consent is obtained, participant questions are answered, participant tracing information and the information on the participant's contacts are updated, and the medication bag is logged and labeled.

Prior to the participant's visit information on mobility and special needs recorded on the PSA form are transferred to Exam Checklist (also referred to as itinerary sheet). The Exam Checklist is not a form in CDART but used on paper, and accompanies the participant from station to station during the field center exam. *Attaching a label of the participant's ID number and the barcode of the ID provides a useful tool for ensuring the correct ID is scanned into fields in non-CDART software, such as the Zeno gait mat software or the ActiGraph initialization software.* At the time of the participant's arrival at the reception station, staff displays the CIU form in CDART and confirms the identifying information, address, and contact information with the study participant. The PSA form is filled prior to the exam visit, during the recruitment or the appointment or reminder call, to alert field center personnel of any special needs and any self-reported conditions that represent exclusions from an examination for safety reasons. At the reception station conditions noted on the PSA form are confirmed with the participant; if not completed previously the PSA form is administered by qualified staff. This can happen immediately after the Informed Consent has been administered.

All exclusion conditions are recorded on the Exam Checklist, which is attached to the participant's folder labeled with his/her name. After the medication bag is labeled, its contents are inspected with the participant to determine if it contains any medications that require refrigeration. Medications requiring refrigeration are labeled with the participant's ID number and placed in the refrigerator. The location of the medication is noted on the Exam Checklist.

As soon as the initial steps of welcome and reception mentioned above have been addressed and participants are comfortable, they are given the opportunity to read and review the informed consent in consultation with ARIC personnel, as described in the next section. No data collection can take place before informed consent has been obtained.

If the field center provides a gown, robe, smock or loose-fitting clothing to be worn during the examination, once the consenting procedures are complete participants are shown where to change clothing. All participants are reminded to remove jewelry, to place clothing and valuables in a secured locker, and to keep eye glasses with them. For visits when blood is drawn, at this point the participant is reminded of the need to collect a urine specimen. The following script can be used:

> "As we mentioned at the time we scheduled your visit we need to collect a urine sample. You may do that as you change clothes for the exam. If you wish to do it later, please notify us when you need to use the bathroom; we can take your urine specimen at any time."

The procedures for the collection of the urine specimen are described in ARIC Manual 7, and are reviewed with the participant.

Staff are trained for the reception workstation by the Study Coordinator at each field center. Certification requirements include the training on general interviewing techniques, administration

of the Informed Consent, the Informed Consent Tracking (ICT) form, and the ARIC data entry system. Although there is no formal certification process for staff at the reception workstation, personnel working at the reception workstation is observed by the local study coordinator for quality assurance and standardization.

7 Informed Consent

Informed consent is the first form administered during the course of the examination. Its core content complies with guidelines from the National Heart, Lung, and Blood Institute and the ARIC Steering Committee. Its content and format also meet the specific requirements of each field center's Institutional Review Board.

Informed consent is obtained at each ARIC cohort examination, to inform the participant of the purpose and procedures of the study and the voluntary nature of their participation. Further, this form is intended to protect the rights of the ARIC Study participants, meet local Institutional Review Board requirements, and to identify the participant's instructions for the type of information and biospecimens to be collected, their long term storage and disposition, and their wishes for sharing their data. The informed consent makes the study participant aware of the right to withdraw from the study, to not participate in a procedure, or to decline to answer any question(s) without penalty. Also at this time the participant is asked for authorization for subsequent contacts by ARIC personnel, to access information in their medical records, and for instructions on distribution of their ARIC study results.

7.1 ADMINISTRATION

The purpose of the ARIC study and the measurements to be made at this exam visit are reviewed with the participant. After introducing the consent form to the participant in a private area, staff asks whether the participant prefers to read the consent form or to have it read by the staff person. Record this preference on the Exam Checklist to make this information accessible to interviewers throughout the clinic visit and avoid repeated questions whether the participant is comfortable reading. Questions are encouraged, and time is allowed for the person to read and sign the informed consent document. Before proceeding, assess whether the participant uses reading glasses or a hearing aid. Record this information on the Exam Checklist and explain to the participant how to have the hearing aid / reading glasses conveniently and safely available throughout the clinic visit.

At the field centers' discretion, the informed consent can be mailed to the participant in the course of recruitment/exam scheduling. Staff should be attentive to the possibility that participants may have read the informed consent prior to their arrival. Questions of clarification should be solicited also under these circumstances and the consent portion of the form must be filled out and signed in the presence of the staff person who serves as witness. If a participant is visually impaired or otherwise incapable of reading the study description and informed consent page, the narrative portion is read to him/her and then the participant is asked to sign the document. The original informed consent document is filed in the participant's study folder. A copy of the informed consent is given to the participant.

7.2 TRAINING AND CERTIFICATION

Study coordinators are responsible for providing local staff training and certification by the Study Coordinator is required. Quality assurance is provided at each field center by means of observation by the local study coordinator.

7.3 DATA COLLECTION

The Informed Consent is a paper form. When the participant receives a copy of the informed consent, the field center has the option of providing a copy of the entire form, or merely the signed consent pages. In all cases, the original signature page must be kept at the field center and stored in the participant's study folder. Any restrictions noted on the informed consent form are keyed into the ICT form (see below).

7.4 ABILITY TO COMPREHEND THE INFORMED CONSENT

Although the capacity to provide informed consent is required for an ARIC examination to be conducted in an ethical manner it can be challenging to identify individuals who may not have the ability to comprehend the informed consent. There are no nationally recognized standards for this assessment and somewhat different findings have emerged when some states (and courts) have taken up this issue. As a result, each field center follows the guidance of its local IRB on whether specific procedures are required for identification of such individuals. For instance, for participants in whom capacity to consent is uncertain, sites may be required to complete a University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) to determine whether the participant can consent for themselves or whether a proxy is required to sign the consent form.

Unless impairment is obvious, recognizing cognitive impairment in a participant is difficult (even for professionals), particularly since social skills can remain intact for participants who otherwise do not perform well on testing. As an added consideration, decision-making capacity is frequently task specific. As a result, depending on the type and extent of impairment, cognitively impaired individuals can remain fully capable of making a variety of decisions, including whether or not to participate in a study. Field center personnel need to be attentive to indicators of potential cognitive impairment, such as repetition (i.e., repeating questions/stories over the course of just a few minutes) and empty or poor responses (i.e., the participant who frequently responds with "I don't know"). Individuals who seem to always be looking to their spouse or a companion for answers to historical questions or medical history questions also warrant consideration for a reduced capacity to answer all ARIC questionnaires.

Unless an IRB specifies specific procedures for vulnerable individuals there is need for guidelines common to the ARIC field centers to provide an environment that assists participants in comprehending the informed consent. To ensure that participants understand the informed consent staff can ask the participant to explain back (in their own words) certain portions of the study. This can be introduced by stating that it is very important that the participant understand his/her rights and the process by which the ARIC study protects the confidentiality of the participant’s information. If the responses from the participant suggest that he/she has difficulty comprehending the consent process or the form contents, the staff person brings this to the attention of the supervisor. If it is determined that a consent proxy needed, but such an individual did not accompany the participant to the visit, the participant will need to be rescheduled to a time when a proxy can be present. .

7.5 ARIC/NCS INFORMED CONSENT PROXY AND INFORMANT TRIGGERS

All ARIC study participants signed an informed consent at baseline, updated at each re-examination, or subsequently through specific instructions provided by the participant to ARIC

that modify or revoke their informed consent. The mechanism by which ARIC monitors and implements the instructions from study participants for use of their data (or future contacts) is the ICT form. The ARIC/NCS examination provides the opportunity to update the ARIC informed consent to current standards of ethical conduct of research, and to tailor the informed consent materials to the study participant's willingness and ability to provide an informed consent. Until a cohort member has signed a new informed consent form, such as Visit 8, his/her informed consent of reference is the most recent informed consent provided to ARIC from the previous ARIC/ARIC_NCS exam visits, the ARIC Brain MRI Study, or the Carotid Artery MRI Study (ARIC CarMRI).

Cognitive deficits may affect the ability to provide informed consent and accurately respond to interviews and questionnaires. Given the age of the ARIC cohort and the increasing risk of cognitive impairment formal procedures are implemented to identify participants: (1) considered vulnerable due to diminished capacity, in particular reduced decision-making capacity to provide informed consent, and (2) with cognitive impairment sufficient to call into question their ability to provide accurate self-report. Those deemed to have diminished capacity to provide informed consent require consent from a proxy to participate in the ARIC study, as well as assent by the study participant. In addition, access to a knowledgeable informant who can assist with interviews and questionnaires is requested for participants whose self-report may be suspect. Staff should encourage the participant him/herself to respond to the questionnaire items unless the participant is unable to do so.

7.6 DEFINING THE NEED FOR PROXY CONSENT OR AN INFORMANT

A proxy is a person authorized to act on behalf of an adult not capable of giving consent. Although some variation exists by state, persons favored to serve as a proxy in order of priority are a Legally Authorized Representative, such as a Health Care Agent or Legal Guardian; a spouse; adult child; adult sibling; friend or other relative. ARIC does not require that a proxy participant – who signs an informed consent on behalf of the ARIC participant – be a Legally Authorized Representative or a Health Care Agent, or Legal Guardian. Local sites should follow requirements specified by their local IRB for determining capacity of consent. For instances, some local IRBs may require completion of a UBACC to determine whether the participant can consent for themselves or whether a proxy is required to sign the consent form. Local policies supersede ARIC-specific procedures presented herein.

An informant (or "alternate informant" or "proxy informant") is a person sufficiently familiar with the participant's daily activities to be able to provide information on the participant's performance. If sufficiently familiar with the participant's performance in the course of daily activities, a proxy participant may also serve as an informant. Classifying decision-making capacity is challenging, and may be task specific. Given the minimal risk associated with the ARIC procedures, conservative criteria are suggested as triggers for requiring proxy consent. See Figure 3.1 and Table 3.1 for information on how to assess the need for proxy/informant participation.

7.7 ADMINISTRATION OF THE INFORMED CONSENT BY PROXY

The ARIC informed consent by proxy is used to obtain informed consent for members of the ARIC cohort whose participation requires a proxy. It is important to identify the need for

participation by proxy prior to the ARIC examination visit so that the participation of the proxy can be scheduled and the appropriate informed consent form be administered. If the need for a proxy becomes apparent only at the time of the ARIC examination the visit must be discontinued until an informed consent by proxy has been obtained.

7.8 CONSENT TRACKING FORM

Within the consent document, participants (or proxies) can specify their level of involvement in the study and how they want their data used (e.g., by for-profit entities). The ICT form is an internal form to track study participants consent to participate and all restrictions specified by the participant (see ICT form). This form tracks each participant's type of consent (full or partial), restrictions on use or storage of DNA, type of restrictions on the participant's data for different types of research questions, the ability to share de-identified data with investigators not affiliated with ARIC, or restrictions on the release of results to participant's physician and permission to access medical records. The tiered informed consent section of the consent form lists separate items asking the participants to indicate whether they agree/disagree to certain procedures and ARIC policies. The participant's instructions for each of these items are recorded on the ICT. This form must be completed in CDART within 3 days of the examination, since this form must be in the database for the ARIC CC and central laboratories (for visits when biospecimen collection is taking place) in order to implement the assay and specimen storage procedures according to the participant's specifications as recorded on the informed consent form.

The ICT includes an additional question (item 10 on the ICT), to record whether the participant restricted access to his/her medical records. For some field centers, this is a question on the consent form. For other field centers, it is based on information included in the body of the informed consent form under the heading 'How will my medical records help ARIC?' (Pagination of the informed consent form may differ across centers).

ARIC participants have granted ARIC personnel access to their medical records since the inception of ARIC, as stated again in the consent form. If the participant does <u>not</u> consent to give access to his/her medical records, the pertinent sentence or paragraph in the informed consent form signed by the participant is crossed out, and initialed by the participant. If any portion of the section titled 'How will my medical records help ARIC?' has been amended or restricted by the participant, Item 10 of the ICT is answered *Do Not Agree*, and a note log is added to this item to list the restriction in a few words. For example, note log entries could mention 'No hospital records', 'do not contact physician's office', 'do not contact next of kin in case of death', 'does not allow use of SSN'. Item 10 of the ICT is answered *Agree* if this section of the informed consent was <u>not amended</u> in the process of obtaining informed consent.

7.9 PROCEDURES TO FOLLOW DURING THE ARIC EXAM IF A PARTICIPANT RESTRICTS CONSENT

Any restrictions a study participant has placed in his/her informed consent to portions of the examination or limits on the use of the data or blood specimens are recorded by field center personnel in the ICT form, as mentioned in the previous section. Based on the ICT form the ARIC CC keeps an updated record of each study participant's instructions in a central database, which is shared in an anonymized format with the ARIC laboratories and reading centers so that their work can conform to the dispositions of the study participant. At the time of data analysis

for publication, restrictions to study records based on the ICT are also communicated to the analysts and users of the ARIC data.

If a study participant refuses specific questionnaires or measurements, the corresponding data collection form(s) are recorded in CDART as permanently missing. A different procedure is followed for the collection of the biospecimens and their processing, during visits when biospecimen collection is taking place. If a participant refuses to donate blood or urine to ARIC, the specimens are not collected (and the reason for the missing data is recorded in CDART). However, no changes are made to the biospecimen collection and processing protocol if a participant has restricted the use of DNA, another specimen or lab test, or to the options to share their genetic material and data. In such a case, all tubes are collected, processed and shipped following the instructions set out in Manual 7. Adjustments to the sample processing, storage and disposition of a participant's biospecimens are then done at the central laboratory, according to the instructions recorded on the ICT form at the field center.

7.10 PROCEDURES TO REMOVE A PARTICIPANT FROM THE STUDY

It is possible to remove a consented study participant for administrative reasons if the field center lead investigator notifies the CC that one or more of the following conditions are true:

- The participant's informed consent was invalid due to cognitive impairment, substance abuse, or equivalent;
- The informed consent was revoked by the participant, wishing a full withdrawal from the study and no further contact.

The CC and field center Principal Investigator work together to ensure appropriate action is taken.

Threatening / antisocial behavior by the participant towards the staff or other study participants can result in a participant being no longer invited to take part in clinic visits, annual and semi-annual phone calls, or excluded from the study entirely. Again, the field center Principal Investigator and CC work together to ensure appropriate action is taken, and reflected in CDART records.

8 Biospecimen Collection (BIO)

ALSO SEE ARIC MANUAL 7

The procedures used for the collection, processing and shipment of blood samples and urine samples are described in Manual 7. The following information provides a brief outline.

Biospecimen collection, including urine and blood samples is part of the protocol for visits 9 and 11. Saliva collection is part of the protocol for visit 10. The information in this section is relevant only to exams that include bio-specimen collection.

8.1 COLLECTION OF THE URINE SPECIMEN

The procedures used for the collection, processing and shipment of blood samples and urine samples are described in Manual 7; following is a brief outline. A urine sample is collected from each participant. After participants complete the reception work station activities and are taken to change clothes, they are informed about the urine collection. After consent, the participant is asked to void a urine sample at the beginning of the clinical exam. If the participant has not voided by the time of the exit interview, the participant is asked to void at that time. A specimen cup (labeled with the participant's ID), cup lid, and a Time Voided label are provided by the staff member working with the participant at that time. The participant is instructed to:

- Void in the cup, filling it if possible, and place the lid securely on top of the container,
- Record the time of voiding on the label, and
- Bring the specimen cup back to the staff member, OR
- Place the sample container in a refrigerator designated for urine samples, and report to a staff member that the specimen has been collected, depending on locally approved OSHA regulations.

Further scripted instructions are provided in Manual 7.

Labeled urine samples should be placed in the designated specimen refrigerator for storage prior to processing and as soon as possible after the specimen has been voided. Procedures are set up at each field center to verify that urine samples are not inadvertently left out at room temperature (the urine specimen may be left at room temperature for no more than 4 hours).

8.2 BLOOD DRAWING AND PROCESSING

Specimen samples are collected and processed by the technicians at each of the four ARIC field centers according to a common protocol. The collection, processing and shipment of blood samples are described in Manual 7. For this examination of the ARIC cohort specimens are shipped for assay and long term storage at two central laboratories: the ARIC Atherosclerosis Laboratory at Baylor College of Medicine in Houston, TX, and the ARIC Clinical Chemistry Laboratory at the University of Minnesota in Minneapolis, MN. A list of the tests performed at these laboratories is provided in Appendix 1 of Manual 7.

A critically important step in this process (and potentially the most difficult to standardize) is the collection and processing of the blood samples at the field centers. Laboratory tests can be repeated, but if the blood sample itself is not correctly drawn, labeled, and processed, the laboratory results cannot be accurate. For the study to succeed, it is important that variation in

measurement values reflect true differences between the study participants rather than differences in blood drawing or specimen processing procedures. Thus, it is important that all field center technicians are well-trained, certified, and fully compliant with the protocol for drawing and processing the specimens in the field.

8.3 COLLECTION OF THE SALIVA SAMPLE

When saliva is collected at the time of an ARIC visit examination (either at the ARIC center or collected at the participant's home), ARIC staff should refer to the protocol for processing, shipping and logging the saliva samples specified in an Appendix of Manual 7 (Biospecimen Collection and Processing). The saliva specimen is collected at the time of the urine or blood specimen collection, unless local circumstances prevent this. Saliva samples may be collected within 30 days of a study participant’s blood draw for ARIC. As noted in Section 5.7, saliva samples are not collected again following an initial collection in the case of split or repeat visit examinations. If a successful blood draw was completed but a saliva sample was not obtained at the time, the study participant is not rescheduled in order to obtain a saliva sample.

8.4 STAFF CERTIFICATION REQUIREMENTS

The blood collection and processing is performed by ARIC-certified technicians at each field center. The field center technicians complete a training course taught by certified central laboratory staff. Each field center technician must complete the training and pass both written and practical exams before becoming ARIC-certified. Re-certification takes place annually, or sooner if a technician does not meet standards as shown in quality assurance and quality control analyses conducted by the CC for the Quality Control Committee (QCC).

9 Anthropometry (ANT)

Anthropometric measures include weight, waist and hip circumference and body fat. These measures are used to assess the relationship between overweight and risk of disease. Height and body size (waist and hip measurements) are not measured at the current ARIC visit examination.

9.1 EQUIPMENT AND SUPPLIES

The equipment and supplies necessary for body measurements are as follows:

- Tanita Body Composition Analyzer, model TBF-300A or TBF-400
- (Wall mounted stadiometer is part of the ARIC workstation, but not used this Visit)
- Full length mirror
- Balance weight scale (available at all times as back up)
- Calibration weights (10 kg)

9.2 STAFF

It is preferable to have an examiner and recorder for each procedure. Technicians are trained to perform both roles. If necessary, a technician may perform the measurements and enter the data into the ANT record in the data management system (CDART). The examiner is responsible for positioning the participant, taking each measurement, and calling the measurement aloud to the recorder. The recorder keys the information into CDART and asks the examiner to confirm or re-measure any out-of-range messages identified by the data entry system. Otherwise, the examiner proceeds to the next measurement in the sequence established by the protocol. The participant remains on the instrument (or the measuring tape remains on the participant) until the recorder enters the measurement in CDART.

9.3 ANTHROPOMETRY FORM

The ANT form records anthropometry measurements in three sections: ability to stand (A), height (not measured in current visit examination), weight, bio-impedance output values from the Tanita scale (C), and waist circumference (D; not measured in current visit examination). As the technician progresses through the examination procedures, they record (or directly enter) results into the ANT form.

9.4 EXAMINATION PROCEDURES

The measurements include body weight, bioimpedance and waist and hip girth. For all measurements, participants should wear light, non-constricting clothing and slippers or socks, but participants must be barefoot when measuring weight and body composition with the Tanita scale.

a. Standing Height

Not performed at current visit. However, the participant's height (in centimeters) measured at the ARIC examination closest in time must be available to key this information into the Tanita panel; see below.

While height is not being measured at the visit, if a participant is curious and asks that you measure their height, please do so. There is no formal protocol for this measurement, and it will not be recorded. If participants are curious about why prior height measurements are being used rather than new measurements, please inform them that prior adult height measurements are more accurate to use when calculating some important CVD risk factors (e.g., body mass index).

b. Weight and Body Composition

If the participant cannot stand on both feet unassisted, ask the participant their weight and record it on the self-reported weight section of the form, rounding to the nearest lb or kg. Participants may choose to report their weight in pounds (lb) or kilograms (kg) and the technician records the information on the form in the units provided by the respondent (Section B).

The participant's weight and body composition analysis are measured using the Tanita scale. This scale calculates the weight of the participant and using a bioelectrical impedance method provides percentage body fat, fat mass, lean body mass and total body water. All these measures are recorded on the form in section B. Record weight to the nearest pound, rounding down if the measurement is 0.5. The control panel of the Tanita scale is depicted in Figure 9.1. A number of settings must be specified before using the scale for the first time. Once the settings are selected, these are recorded automatically and there is no need to make changes. Just press ON/OFF key to start.

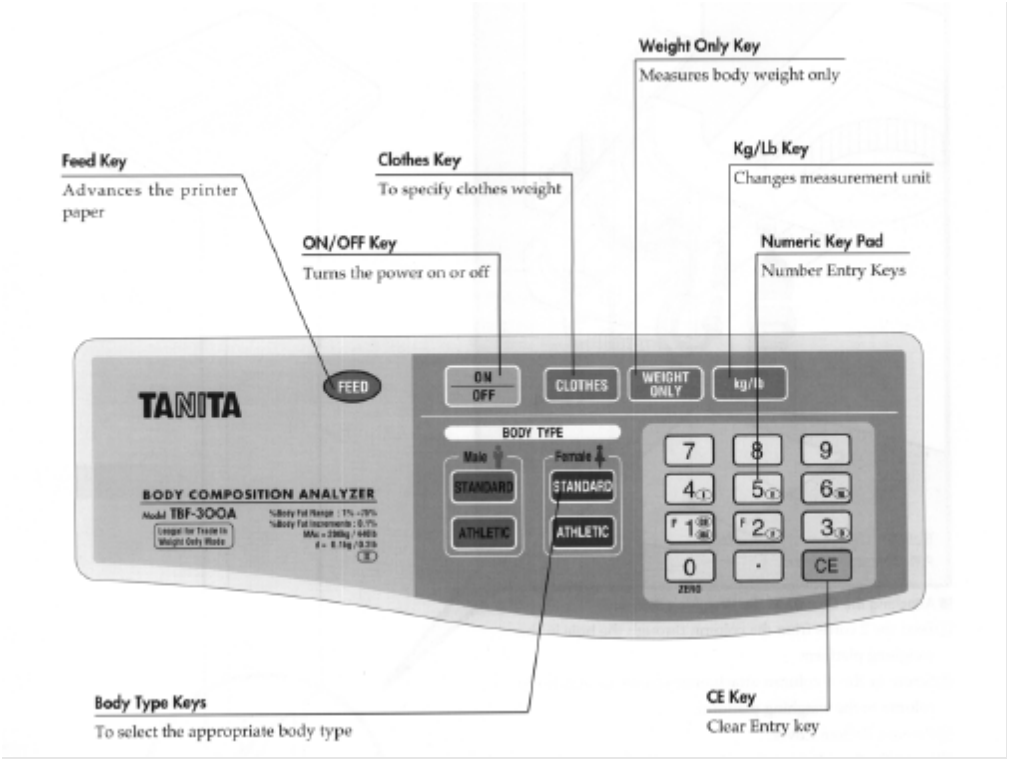


Figure 9.1. Control Panel of Tanita Body Composition Analyzer, TBF-300A

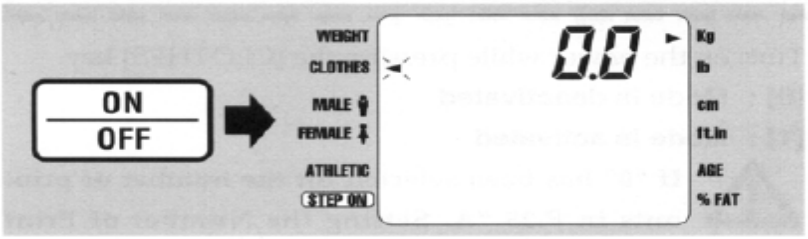
c. Initial set up

Place the scale platform on a flat and level surface, not on a carpet. Don't worry if balance bubble indicates it is not exactly level. Connect the keyboard to the scale with the gray cord attached to the scale and plug it into the back of the keyboard in the socket marked "input." Connect the keyboard to an electrical outlet using the black power cord and AC adapter. Plug the black cord into the socket on the back of the keyboard marked "DC5V."

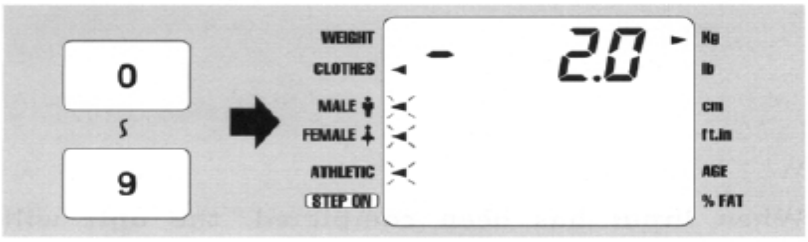
d. Setting the number of print outs and printing language

Press and hold the 0 key, and press the ON/OFF key once. Release the 0 key after "Prt-1" is displayed on the screen. Select 0 (no print out). When no print out is selected (there is no need to select the printing language). The panel will switch to the measurement screen.

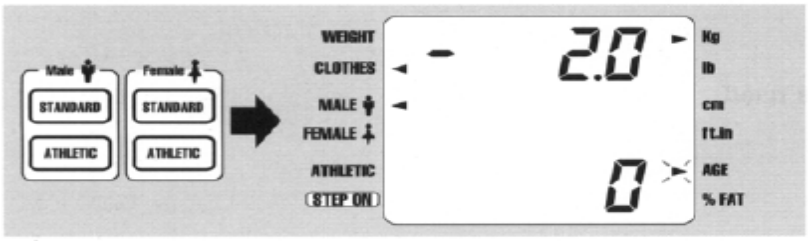
e. Operating instructions



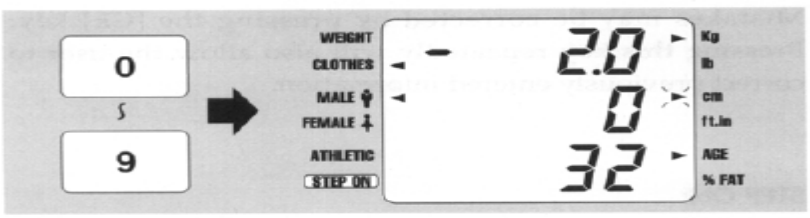
Press ON/OFF key to turn the machine on. Wait until 0.0 and an arrow appear on the screen. Check that the arrow points to "Kg". If arrow point to "lb", press the Kg/Lb key on the control panel and the arrow will shift to "Kg"



Enter Clothes weight: 1.0 kg using the numeric pad on the control panel

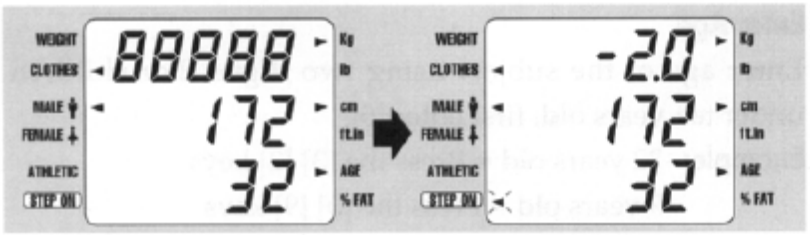


Select Gender and Body type: Standard Female or Standard Male

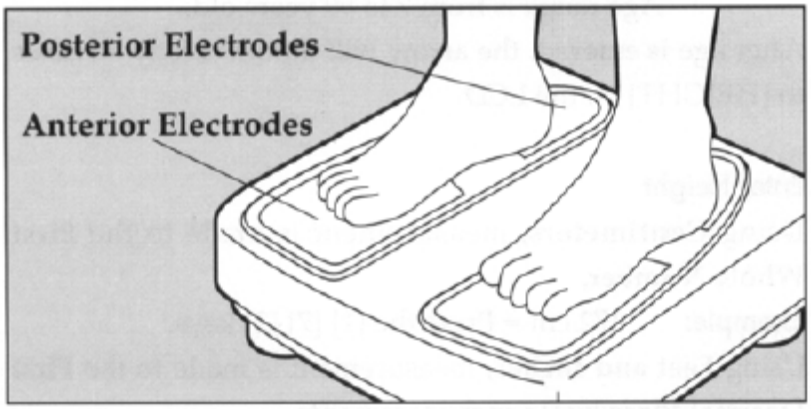


Enter age of participant using the numeric pad of the control panel. After age is entered, the arrow will direct you automatically to enter the height.

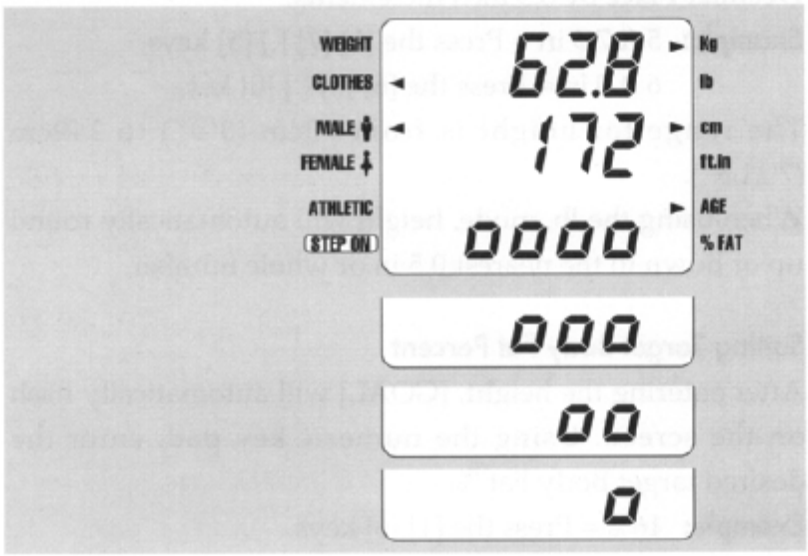
Enter height in cm. For example, for 172 cm, press the [1] [7] [2] keys.



Mistakes may be corrected by pressing the [CE] key. Pressing this key repeatedly will allow correcting the previous information



Wait until the screen displays “88888’ and then ask the participant to step on the scale. Participants should be bare-foot. Each foot should be touching both the heel and toe plates, with weight evenly distributed on both feet.



Weight will be displayed on the upper section of the screen.

After weight stabilizes, impedance measurement is taken. Bubbles “oooo” will appear on the bottom half of the screen as these measurements are being analyzed. Once body composition measurements are ready, the bubbles will disappear one by one. Record weight and each body composition measurement including impedance on the Anthropometry form. Ask the participant to step off

If the screen returns to ---- for weight, the participant weighs more than 440 lb. Record 999.9 for weight and 99.9 for % body fat on the data form. If screen returns error messages **E-01** or **E-16** it means that the unit could not get a good reading, either because: 1) the participant stepped off the scales before the beep; or 2) the participant is wearing socks or has thick calluses on his/her feet. If the problem appears to be #1, repeat the measurement procedure. If the problem appears to be #2, place a drop or two of saline on each scale plate to help signal conduction. If the error messages appear again after adding saline, turn the unit off, turn the unit on, press **WEIGHT ONLY**, and only record a weight on the data form. Record **99.9** for % body fat on the data form.

Once measurements are completed, the machine will automatically return to the Gender and Body Type screen in about 10 seconds. Leave keyboard on. Wipe off plates on scale with antiseptic wipes. The next participant can now be measured.

> ***IMPORTANT SAFETY ALERT:*** *PARTICIPANTS WITH A PACEMAKER, A DEFIBRILLATOR OR OTHER INTERNAL ELECTRONIC DEVICE, SHOULD BE MEASURED IN 'WEIGHT ONLY' MODE, OR ON A REGULAR, CALIBRATED SCALE*.

Do not weigh participants who have a cast, if larger than a finger splint, that cannot easily be removed or that the participant is comfortable removing. If a participant has a prosthetic limb, measure weight with limb in the "Weight Only" mode, make a note in the comment section of the form. In the event of a power outage or if the scale is not functioning properly, use the balance scale as back-up and notify the project coordinator.

f. Abdominal (Waist) Circumference

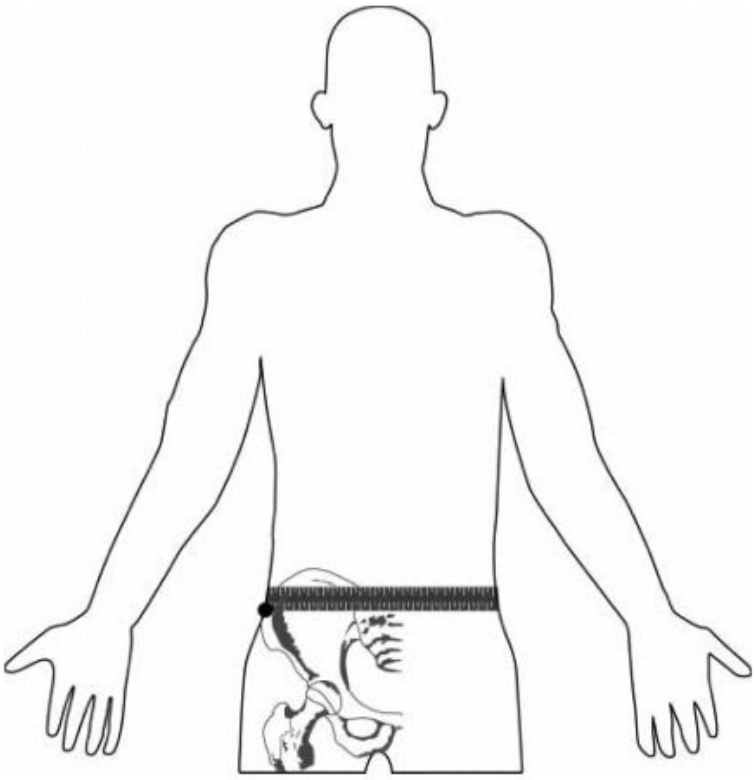
For visits collecting waist circumference measurements, the procedures should be completed as follows. To define the level at which the abdominal circumference is measured, first locate and mark a specific bony landmark, the lateral border of the ilium. Have the participant stand and hold their shirt above the waist. Lower the pants and underclothing of the participant slightly, and standing behind and to the right of the participant, palpate the hip area to locate the right ilium (see Figure 9.2). Draw a horizontal line just above the uppermost lateral border of the right ilium and then cross the line to indicate the mid-axillary line of the body. Standing on the participant's right side, place the measuring tape around the trunk in a horizontal plane at the level marked on the right side of the trunk. Hold the zero end below the measurement value. Use the mirror on the wall to ensure horizontal alignment of the measuring tape. This is especially important when measuring overweight participants or women with hourglass-shaped torsos. The recorder (if available) makes sure that the tape is parallel to the floor and that the tape is snug, without compressing the skin. Measurements are made at the end of a normal expiration and reported to the recorder to the nearest centimeter (rounding down if 0.5 cm), and entered in section D of the form.

g. Hip Circumference

For visits collecting hip circumference measurements, the procedures should be completed as follows. Instruct the participant to stand erect but relaxed, with weight distributed equally over both feet. The hip girth is measured at the level of maximal protrusion of the gluteal muscles (buttocks). Verify this position by passing the tape above and below the observed maximum. Keep the anthropometric tape horizontal at this level and record the measurement to the nearest centimeter. The tape should be snug, but not tight enough to compress tissue. The measurement should be made from the participant's right side. Only one measurement is made.

The greatest source of error for this measurement is due to a tape that is not horizontal. Before making the measurement the observer verifies the position of the tape from both the front and back to assure its correct position and verifies that the tape is horizontal. In the absence of a recorder, the technician uses the wall mirror to confirm that the tape is horizontal. Record the results to the nearest centimeter (rounding down if exactly 0.5 cm).

Figure 9.2. Measuring Tape Position for Waist Circumference



9.5 QUALITY ASSURANCE AND QUALITY CONTROL

a. Calibration Procedures and Equipment Check

Anthropometry equipment is calibrated frequently and results are recorded on an Anthropometry Equipment Calibration Log. The Tanita scales are zero balanced daily and calibrated weekly or when moved. Calibrate the scale by pressing **WEIGHT ONLY** key, making sure the arrow pointing to weight is in Kg units. Place the calibration weight (10 Kg) in the middle of the scale, and when the digital display has stabilized record the weight indicated on the LED in the daily log. The values should be within 1.5 kg of the expected weight. If the calibration weight is less than 8.5 kg or more than 11.5 kg, use the back-up scale, and 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. Copies of the equipment logs may be requested by the CC. Turn off scale by pressing the ON/OFF key since the unit needs to be turned off after running in the “WEIGHT ONLY’” mode before it can be used for body composition determinations. Examine the anthropometry tapes on a weekly basis for signs of wear.

b. Training, Certification and Quality Control

All data collectors taking anthropometric measurements must be certified by successfully completing training requirements. Training and practice sessions will be conducted prior to certification. A trained technician who passes certification criteria can train and certify other

technicians at the field center. Study personnel certified in all anthropometric measures procedures for a prior visit are considered certified for the visit immediately following. Certification testing requires a minimum of five 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.

Newly certified technicians are observed by the study coordinator twice during the first month following certification and then twice per year to ensure standardization. The Supervisor Checklist for Observation of Anthropometry Measurements 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. A minimum of 4 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. Repeat measurements for quality assurance by the same or different ARIC technicians are not done as part of visit examinations after Visit 6.

10 Sitting Blood Pressure (SBP)

10.1 INTRODUCTION, EQUIPMENT AND SUPPLIES

Accurate blood pressure measurements are critical for the estimation of the prevalence of high blood pressure and for tracking the incidence of hypertension. For many years the “gold standard” blood pressure measuring device has been the mercury sphygmomanometer. However, because of the increase in awareness of the serious adverse health effects of mercury contamination in the environment, more and more institutions, including the National Institutes of Health, have banned or discouraged the continued use of mercury sphygmomanometers and thermometers. Further, the Environmental Protection Agency (EPA) and the American Hospital Association (AHA) took steps to eliminate mercury-containing waste by 2005. For these reasons, increasing numbers of institutions and clinics have switched to alternate sphygmomanometers such as aneroid or automated devices that do not contain mercury. Furthermore, it is important that ARIC measurements be directly comparable to other national studies such as the NHANES. In line with these developments and for the best repeatability of measurements, a tested, automatic sphygmomanometer (the OMRON HEM-907 XL) is used in ARIC. This model has been validated in other studies, including CARDIA and NHANES, and more recently ARIC.

Note: Seated blood pressure should be measured early in the sequence of visit examinations as it may detect an actionable, elevated blood pressure without delay.

Field center technicians are responsible for verifying that all equipment and supplies are in the examination room, at all times.

Equipment	Supplies
OMRON HEM -907XL sphygmomanometer	Wipes
4 cuffs	Alcohol
Gulick II tape measure	Tissues
Foot stool	Water soluble ink pens
Room Thermometer	Gauze (4 x 4)

Figure 10.1. OMRON HEM907XL sphygmomanometer and 4 cuffs

OMRON HEM907XL with four cuffs

10.2 THE SITTING BLOOD PRESSURE (SBP) FORM

The SBP form records arm measurements used to guide blood pressure cuff size selection and serial measurements of both blood pressure and pulse rate. The form is divided into five corresponding sections: (A) Arm Measurements and cuff size selection, and (B-E) and the Average First-Third Blood Pressure / Pulse Rate.

10.3 BLOOD PRESSURE MEASUREMENT PROCEDURES

The technician greets the participant and explains that his/her blood pressure will be measured next. To choose the appropriate cuff size the participant's arm will be measured first, followed by a period of quiet rest and then three blood pressure measurements taken by a machine. The display of the OMRON machine is turned away from the participant, to avoid reactive blood pressure responses if a participant observes his/her blood pressure. The participant is reminded that the results of the measurements will be provided at the end of the visit with a printed report, and the technician asks if the participant has questions before proceeding.

a. Selection of the Arm

For the purpose of standardization, both pulse and blood pressure are measured in the right arm unless specific participant conditions prohibit the use of the right arm, or, if participants self-report any reason that the blood pressure procedure should not use the right arm. If the measurements cannot be taken in the right arm, they are taken in the left arm. Use of the right or left arm must be recorded on the SBP form in Item A.1. Measurements are not done on any arm that has rashes, small gauze/adhesive dressings, casts, are withered, puffy, have tubes,

open sores, hematomas, wounds, arteriovenous (AV) shunt, or any other intravenous access device. Also, women who have had a unilateral radical mastectomy do not have their blood pressure measured in the arm on the same side as the mastectomy was performed. In the instance of women who had a bilateral mastectomy, ask the women whether she has lymphedema in both arms. If she does not, ask if she has any concerns about blood pressure measurements in the arm with no lymphedema. Do not conduct blood pressure measurements in an arm with lymphedema, or if the woman has concerns. In all cases, if there is a problem with both arms, the blood pressure is not measured.

b. Cuff Size Selection and Application

It is important to select the appropriate size cuff that properly fits the participant's arm. The length and width of the bladder inside the cuff should encircle at least 80 percent and 40 percent of an arm, respectively. The index lines on the cuff are not used in this study. Using a centimeter tape, determine the midpoint of the upper arm by measuring the length of the arm between the acromion and olecranon process (between the shoulder and elbow).

c. Measurement of Arm Circumference

- Have the participant remove his/her upper garment or clear the upper arm area so that an unencumbered measurement may be made.
- Have the participant stand, with the right arm hanging and bending the elbow so that the forearm is horizontal (parallel) to the floor.
- Measure arm length from the acromion (bony protuberance at the shoulder) to the olecranon (tip of the elbow), using the Gulick II anthropometric tape.
- Mark the midpoint on the dorsal surface of the arm.
- Have the participant relax arm alongside of the body.
- Draw the tape snugly around the arm at the midpoint mark. NOTE: Keep the tape horizontal. Tape should not indent the skin.
- Measure and record the arm circumference in centimeters on the SBP form in Item A.2.

d. Choosing the Correct Cuff Size

Identify the measured arm circumference below and use the cuff size associated with the arm circumference in column 1 of Table 10.1. (Example: If the arm circumference at midpoint is 36 cm, use the large adult cuff marked CL19.) Record the cuff size on the SBP form in Item A.3.

Table 10.1.

Arm Circumference (cm)	OMRON CUFF SIZE
17.0 to 21.9	index 17- 22cm (CS19) - Small
22.0 to 32.5	index 22-32cm (CR19) - Adult
32.6 to 42.5	index 32-42cm (CL19) - Large
42.6 to 50.0+	index 42-50cm (CX19) – X-Large

e. Special Situations / Obese Study Participants.

The length and width of the cuff's bladder should encircle at least 80 percent of the length of the upper arm, and 40 percent of the width of the arm. If the upper arm is relatively short with a large circumference (>50 cm) it may be difficult to fit even a thigh cuff in a way that meets protocol. In this case an appropriately sized cuff is wrapped around the participant's forearm, supported at heart level. The cuff size should be selected according to the forearm diameter, measured at the (approximate) midpoint of the forearm's length. Note: when taking the blood pressure on the forearm reverse the cuff, so that the marker referring to the brachial artery is at the elbow.

f. Record the use of the R/L forearm in item 1 of the SBP form (Other) and add a note log to this effect.

Blood pressures measured on the forearm tend to overestimate the systolic and diastolic pressures, but they provide a good estimate of the systolic blood pressure in circumstances when a cuff is too small for an obese arm, which can lead to misclassification of an individual as hypertensive.

g. Positioning the ARIC Participant and Placing the Cuff

Ask the participant to sit and rest quietly in the chair after adjusting it, if necessary, to allow the participant's feet to rest flat on the floor when the legs are in the uncrossed position. The technician then explains the next steps using the following script: "Before taking your first blood pressure reading, there will be a 5 minute waiting period. When I inflate the cuff, it may feel tight and you will feel some pressure on your upper arm. While we are measuring your blood pressure, we ask you not to talk and I will not talk either because talking and moving could change your blood pressure level. We will give you a report with your blood pressure values at the end of your exam visit. Do you have any questions?"

The right arm and back should be supported and the legs should be uncrossed with both feet flat on the floor. The right arm should be bared and unrestricted by clothing with the palm of the hand turned upward and the elbow slightly flexed.

The arm should be positioned so that the midpoint of the upper arm is at the level of the heart. The location of the heart is taken as the junction of the fourth intercostal space and the lower left sternal border. Small or short participants may have to raise their body to the correct position by changing the chair position up or down. If necessary, especially with short participants, place the participant's feet on the footstool provided to stabilize their feet in a flat position. Very tall participants may need to place their arm on a book or pillow to bring their upper arm to the correct position.

h. Locating the Pulse Points

Figure 10.2. Locating the brachial pulse

Locate the brachial artery by palpation and mark the skin with a small dot, using a black pen. (The brachial artery is usually found just medial and superior to the cubital fossa posterior to the biceps muscle and slightly towards the body). For brachial artery palpitation, fingertips or thumb may be used.

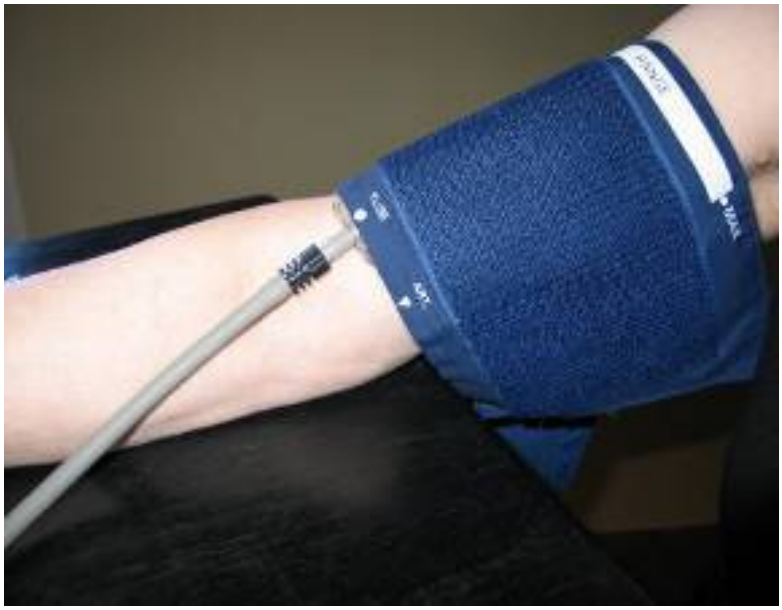
i. Wrapping the Blood Pressure Cuff around the Arm

Position the rubber bladder with the "art" label on the bottom of the cuff, just above the pen mark over the brachial artery pulse determined earlier at least 1" above the crease of the elbow. The cuff tubing should be at the outer (lateral) edge of the arm if the cuff is placed correctly.

For short or fat conical arms: if the cuff that matches the arm circumference is too wide to fit on the upper arm with space above the brachial artery pulse point at the cubital fossa then choose the next smaller cuff size and enter the cuff size chosen on the SBP form in Item A.3.

Placing the cuff (Figure 10.3). Place the "art" marker on the inner part of the cuff directly over the brachial artery. The cuff should be wrapped in a circular manner. Do not wrap the cuff in a spiral direction. Check the fit of the cuff to ensure that it is secure but not tight.

Figure 10.3.



10.4 PROCEDURE FOR THE OMRON HEM-907XL

This protocol is written for use with the OMRON HEM-907XL automated blood pressure monitor. Special attention must be placed on assessment and maintenance of the instrument's accuracy as per the manual that accompanies the instrument. The design and operation of the OMRON HEM-907XL are based upon the combined principles of compression of the brachial artery under an elastic, inflatable cuff and estimation of the systolic and diastolic blood pressure levels by detection of oscillometric waves.

a. Setting up the OMRON

At a start of each session check that the monitor is attached to the AC adapter to the DC jack and plugged in (Figure 10.4) and AC sign (Figure 10.5) is visible in the lower window.

Figure 10.4.

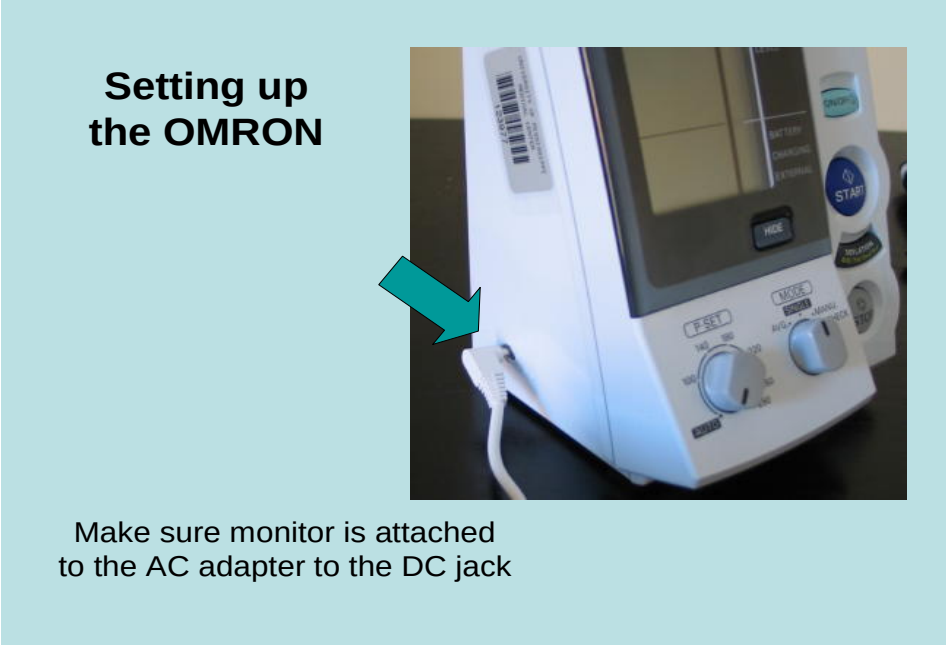


Figure 10.5.

When the power is OFF, push the ON/OFF (power) button for more than three seconds while holding the START button simultaneously: F1 is displayed in the first window and three inflation (3) is displayed in the middle window (Figure 10.6). If needed push the DEFLATION (deflation control)/Measurement Result Display Switch Button to change the set value to 3 inflations.

Figure 10.6.

Push the START button and F2 function is displayed in the first window and 0 waiting time is displayed in the middle window (Figure 10.7).

Figure 10.7.

If needed push the DEFLATION (deflation control)/Measurement Result Display Switch Button and change the set value to 0 sec waiting time. Push the START button and F3 function is displayed in the first window and inflation interval 30 second time is displayed in the bottom window (Figure 10.8).

Figure 10.8.

If needed push the DEFLATION (deflation control)/Measurement Result Display Switch Button and change the set value to 30 sec measurement interval.

Table 10.2 summarizes the needed settings for the exam

Table 10.2

Function #	Items to set	Set value
F1	Number of inflations	3 times
F2	Waiting time to start the first inflation	0 sec
F3	Inflation interval	30 sec

b. Measuring the Blood Pressure

Once these settings are validated the exam can start. Turn off the OMRON by pushing the ON/OFF button. To measure blood pressure in average mode, push the ON/OFF button to turn on the power. Set the MODE selection to AVG, set the P-SET (inflation level) knob to AUTO (Figure 10.9).

Figure 10.9.

AUTO AVG

Next, connect the air tube to the cuff (Figure 10.10).

Figure 10.10.

For all cuff sizes small, medium, large, and X-Large connect the air tube to the main unit by attaching the air plug to the base of the air connector. Connect the cuff to the air tube attached to OMRON unit. Wrap and secure the appropriate cuff to the participant's upper right arm as set out in section 10.3g. , above.

Record the time of blood pressure measurement in Item A.4, then push the START button to start the measurements. The cuff will inflate automatically and deflation will begin after the OMRON detects no oscillometric waves. The dial will show sequentially in the bottom panel of the LCD screen 1st , 2nd , and 3rd measurements with 30 seconds between each listing (Figure 10.11).

Figure 10.11.

After each inflation and deflation, the systolic blood pressure, diastolic blood pressure and pulse rate will be displayed in the top, middle and bottom sections of the LCD screen.

After the first and second measurements are displayed, there will be a preset 30 second interval before the beginning of the next measurement. During this time have the participant raise their cuffed arm above their heads as in Figure 10.12 below for the count of 5 and then return to the original resting position with the arm supported with the cubital fossa at heart level. Do not clench the fist. This is done after the 1st and 2nd measurements, to avoid venous congestion in the arm that may not have dissipated after inflation of the cuff – which in turn could increase the pressure recorded on subsequent measurements.

Figure 10.12

c. Recording the OMRON Results

After all the inflations are finished, the average of the three systolic pressures, diastolic pressures and pulse rates is displayed. Record these average measures on the SBP form in Items E.14-E.16. Push the DEFLATION button to toggle to the first set of measures and record the 1st set on the SBP form in Items B.5-B.7. Repeat this process by pushing the DEFLATION button to display and record the 2nd and 3rd sets of measures on the SBP form in Items C.8-C.10. and Items D.11-D.13, respectively.

> ***Safety Note****: Average heart rate values that are 44 bpm or lower, or 110 bpm or greater, should be brought to the attention of the study clinician on site before the participant leaves the field center. The study nurse or the physician on call should evaluate the possible reasons for an abnormally high or low heart rate and refer the study participant for evaluation by their provider of care or to an emergency department if deemed appropriate.*
>
> *An average heart rate value of 44 bpm or lower, or 110 bpm or greater does not require that a seated blood pressure per the ARIC protocol be repeated. An evaluation performed by a clinician may include a seated blood pressure, which is <u>not</u> recorded on the SBP form.*

Push the ON/OFF button. This terminates the exam and you are ready for the next participant

10.5 REPORTING THE BLOOD PRESSURE VALUES

The participant's blood pressure values are not discussed at the blood pressure station nor during the measurement process. The technician will have informed the participant that the blood pressure values and other results will be printed out and discussed with the participant at the end of the visit. If pressed, the technician can add that the research protocol requires that results not be discussed during the examination. The OMRON display and the computer monitor should be turned away from the participant so that the blood pressure values being recorded are not easily visible.

The average systolic and diastolic blood pressure values are reported to the study participant at the end of the field center examination and also as part of the consolidated report of study results that field centers send to the study participant (and his/her medical practitioner, if so instructed by the participant). In each case the average systolic and diastolic pressure values recorded on the form are retrieved by the data management system and displayed in the report, with the narrative statement that corresponds to that value and whether the participant has reported being on antihypertensive treatment. The blood pressure results are reviewed with the participant during the exit interview, at which time ARIC personnel explain the recommended follow-up for the pertinent blood pressure level according to the recently released 2017 Evidence-Based Guideline for the Management of High Blood Pressure in Adults.

As a participant safety procedure, if the average blood pressure is equal to or greater than 180 mmHg systolic or equal to or greater than 120 mmHg diastolic, the technician tells the participant that the procedure will be repeated as part of study protocol, removes the cuff and locates the brachial artery by palpation as shown in Figure 10.2 of this section, and repeats the blood pressure measurement steps. This second set of blood pressure values is recorded on the form and entered into CDART instead of the first set.

If the average blood pressure of the second set of readings is equal to or greater than 200 mmHg systolic or equal to or greater than 120 mmHg diastolic, the technician closes out the data entry screen per protocol, interrupts the field center examination and notifies the supervisor of this immediate alert situation. With input from the supervisor or clinic manager, ARIC personnel then assist the participant in scheduling a same-day visit to his/her provider of care, or arranges transportation to the nearest emergency room for a medical evaluation of the participant's blood pressure. If the average blood pressure of the second set of readings is in the range of SBP 180-199 or DBP 110-119 the field center examination may proceed, and ARIC staff assists the participant in scheduling an appointment with a medical professional within 48 hours, to determine whether treatment should be started or changed. Section 20.2 of this manual describes the corresponding report of this study result.

10.6 EQUIPMENT MAINTENANCE

Technicians will maintain all blood pressure equipment used in their clinic. The following sections specifically state the steps that technicians follow to check equipment and maintain equipment used for the technician examination.

- OMRON HEM-907XL: Weekly - wipe the monitor with a soft, damp cloth moistened with disinfectant alcohol, or diluted detergent. Complete cleaning by wiping the monitor with a soft, dry cloth.
- Blood Pressure Cuffs: Check the inflation cuff for cleanliness, and wipe between each use with disinfectant wipes. 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.

10.7 INSPECTION AND VALIDATION OF THE OMRON SPHYGMOMANOMETER

a. Daily Check points

- Check function settings on the OMRON machine (0 waiting, 3 inflations, 30 seconds interval between inflations)
- Check Mode and P-setting on OMRON unit
- Make sure that the AC adapter cord of the OMRON unit is securely plugged in (it has a tendency to get disconnected from the unit).
- Check the OMRON unit AC adapter cord and tubing for cracks.
- Clean all the equipment.

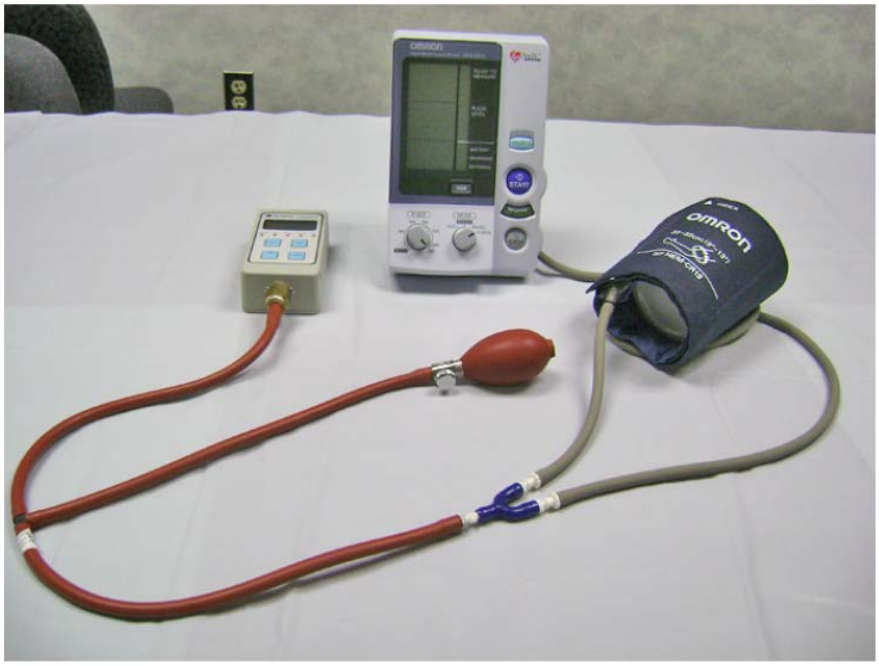
b. Quarterly Validation of the OMRON Sphygmomanometer

Each OMRON unit is checked every 3 months as described in this section. 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 ARIC CC for inclusion in the quality control reports. A sample copy of the maintenance and calibration log is found in the Quality Control (QC) Appendices. The equipment logs are summarized quarterly using the Summary of Observation and Equipment Checklist and may be requested to be sent to the CC.

c. Equipment Required for Accuracy Check

The calibration equipment is the Pressure-Vacuum Meter (Shown in Figure 10.13). Netech DigiMano Digital Pressure/ Vacuum Meter model 2000 for a range of 0 to 300 mmHg). The following adaptors are used and are kept at the field center: Y **tubing** – with 2 arms and an inflation bulb attached to the middle arm of the Y tubing; Y- **adapter** with appropriate male/female connectors; Adaptors for tubing connection; OMRON cuff with short tubing attached. If indicated by the ARIC QCC, once per year each DigiMano device is shipped to the manufacturer for calibration. Completion of this check by Netech is then reported to the QCC.

Figure 10.13.



OMRON Accuracy Testing protocol

The following sequence of steps detail the OMRON accuracy testing protocol.

1. Inspect the OMRON sphygmomanometer for signs of damage to the case, and wall mount bracket if applicable.
2. Inspect the tubing for holes or cracks, which would allow air to leak out. Cracking is commonly found around the connection points to the sphygmomanometer, and cuff. If cracking is seen the tubing is replaced from that point by trimming the damaged area with scissors and reconnecting the tubing. In extreme cases, the entire tubing is replaced.
3. Inspect the cuff(s) for signs of wear and tear to the outer cloth casing and Velcro fabric. Also, inflate the unit (with the cuff connected to the OMRON and wrapped around a rigid cylinder and the OMRON MODE knob set on CHECK) enough to determine if the bladder within the cuff is leak- proof. If leaks or damage are noted to the cuff or bladder, it should be replaced.
4. Disconnect the cuff from the long adaptor tubing that stays connected to the OMRON sphygmomanometer.
5. Connect one upper arm of the Y adaptor to the short tubing from the cuff and attach the other upper arm to the long tubing attached to the OMRON.
6. Connect the bottom arm of the Y **adapte**r to one arm of the Y **tubing**.
7. Connect other end of the Y **tubing** to the pressure-vacuum meter.
8. Turn the pressure-vacuum meter on. Use the accompanying AC adapter if necessary.

9. Following manufacturer's instructions, select "mm Hg" as the type of unit to be tested.
10. Zero the pressure-vacuum meter per manufacturer's instruction.
11. Pump up the aneroid unit to 280 mm Hg. Release the pressure slowly and observe the changing OMRON LED mm Hg for a smooth descent along the range to 20 mm Hg
12. Again, pump the aneroid unit to above 250 mm Hg (but less than 300 mmHg) using the bulb and tighten the valve as tightly as possible
13. Check to see if the aneroid unit is within ± 3 mm Hg of the readout on the pressure-vacuum meter.
14. Continue to compare the readout of the OMRON unit to the pressure-vacuum meter approximately every 20 mm Hg along the entire range – down to 30mm Hg. Variations greater than ± 3 mm Hg requires the OMRON unit be removed from service and repaired or replaced.
15. Record the results of the calibration checks on the OMRON BP Monitor Maintenance and Calibration Log (together with the unit number, the date and the technician ID). You may be requested to send the log to the ARIC CC. A copy of the OMRON BP Monitor Maintenance and Calibration Log is found in the QC Appendices.

10.8 TRAINING AND CERTIFICATION

Blood pressure technicians are trained and certified locally by a certified technician. Certification results from training of new staff at the field centers are submitted using the Certification Request Form (located on the ARIC website under [Cohort > Documents > V9/NCS]) 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. A trained technician who passes certification criteria can train and certify other technicians at the field center. Study personnel certified on the sitting blood pressure procedures for a prior visit are considered certified for the visit immediately following.

The blood pressure supervisor observes each technician responsible for taking blood pressure measurements twice during the first month after certification, and twice per year afterwards. The Checklist for Observation of Blood Pressure Measurements (QC Appendices) is used for each observation. Training and certification programs, observation of data collection by the study coordinator and standard equipment maintenance procedures performed and summarized quarterly onto the Summary of Observation and Equipment Checklist may be requested to be sent to the CC. The CC will also monitor the distribution of readings from the OMRON sphygmomanometer for any irregularities.

10.9 GLOSSARY AND REFERENCES

Systolic blood pressure is defined as the highest arterial blood pressure of a cardiac cycle occurring immediately after contraction of the left ventricle of the heart.

Diastolic blood pressure is the lowest arterial blood pressure of a cardiac cycle occurring during the passive rhythmical expansion or dilation of the cavities of the heart during which they fill with blood.

Auscultatory method detects sounds of pulsatile blood flow in the artery using a stethoscope held over the artery just below an inflated blood pressure cuff. As the blood pressure cuff gradually deflated, pulsatile blood flow is re-established and accompanied by sounds that can be detected by the stethoscope. The pulsatile sound corresponds to a reading of a mercury column (mercury sphygmomanometer) or a dial (aneroid) device connected to the blood pressure cuff.

Oscillometric method uses a transducer to measure the oscillations of pressure in the blood pressure cuff corresponding to the pulsatile blood flow in the artery under the cuff. The oscillometric method is used by all automated blood pressure machine.

11 Cognitive Testing

11.1 OVERVIEW

To identify and characterize dementia and mild cognitive impairment (MCI) in the ARIC cohort, an efficient but comprehensive neuropsychological assessment will be administered by trained and certified examiners (Stage 1 evaluation). The battery of cognitive measures is a set of well-validated, standardized instruments that are widely used in clinical and epidemiologic studies of dementia and cognitive function and include most of the measures recommended in the Uniform Data Set (UDS) implemented in 2005 across all National Institute on Aging-sponsored Alzheimer's Disease Centers.

The neuropsychological battery is designed to assess multiple domains including global cognitive status, memory, language, and executive function/processing speed. Test scores are compared to age, education, and race-specific normative data to identify those with suspected dementia or MCI. Participants who have significant cognitive decline from prior exams and have impairment in any one of the three cognitive domains: memory, language, or executive functioning, will be invited to a Stage 2 evaluation. The criteria for defining dementia/MCI including consideration of significant change (decline) in cognitive functioning required for a diagnosis of dementia/MCI are detailed in Manual 17.

11.2 ADMINISTRATION – OVERVIEW

The neurocognitive tests are categorized into two blocks, A and B. The full battery, blocks A and B, will be administered at Visits 9, 11. The order of test administration is as follows: Block A: ESU, MMSE, NCS tests [DWR (exposure), DSS, DWR (recall), Incidental Learning, FAS, Animal Naming] followed by Block B [Logical Memory I, Digit Span (backwards), Trails A, Trails B, Boston Naming Test, and Logical Memory II]. A brief description of each measure is provided in Manual 17. A list of the test materials and detailed testing procedures including scoring are found in the NCS QxQ instructions.

To minimize the influence of fatigue on the test results the cognitive battery, conduct these tests early in the participant's visit. A trained examiner administers the cognitive function tests in a fixed order, one right after the other, during a single session in a quiet room. The tests are administered following the instructions printed on the Neurocognitive Test Battery Packet and NCS question-by-question (QxQ) instructions. Responses are recorded on the paper test packet by the examiner or by the participant and kept in the participant's folder. Test results are tabulated by the examiner after the participant has completed the tests and left the room. Test results are summarized on the Neurocognitive Summary Score Form and entered into CDART. Selection for Stage 2 is determined by the CC. There will be a modest delay between study start and the availability of the Participant Selection Stage 2 report based on the time it takes to collect ~100 complete, query-free neurocognitive tests (see details in Manual 17 for justification). Once the selection is established, the Participant Selection for Stage 2 Report in CDART returns the Participant IDs who should be contacted for Stage 2 data collection (NPI, CDI, CDS). After the initial delay from study start, the participant's selection status is updated in the database on the Wednesday following neurocognitive testing (the CC retrieves the database each Wednesday).

11.3 STAGE 2 – COGNITIVE STATUS

a. Rationale and Selection to Stage 2

Participants who meet a priori criteria of poor cognitive performance (i.e., those who score poorly in any cognitive domain and show significant cognitive decline from previous visit) are invited to a Stage 2 evaluation based on an informant interview. The participant provides permission to contact an informant during the clinic visit. The informant interview includes the CDR informant interview that provides information about the participant's functional status, and the Neuropsychiatric Inventory that gives information about any neuropsychiatric symptoms the participant may be experiencing. Eligibility for Stage 2 is determined by the selection algorithm, based on information collected using the NCS form. Site staff run a CDART report (Participant Selection to Stage 2 report) which returns the list of participants who are eligible for Stage 2 data collection.

b. Overview

The neurologic interviews completed as part of Stage 2 include the Clinical Dementia Rating Scale (CDR) and the Neuropsychiatric Inventory (NPI). The CDR includes the CDR Participant (CDP, administered to all participants), the CDR Informant (CDI), and the CDR Summary (CDS). In addition, the Functional Activities Questionnaire (FAQ) is used in determining a participant's level of daily functioning but does not have a dedicated interview or form; instead, all FAQ items are embedded within the CDI form. Each of the measures, described in detail in Manual 17, are well-validated, standardized instruments that have been widely used in both clinical and epidemiologic studies of dementia and cognitive function, and include some of the measures recommended in the Uniform Data Set (UDS) implemented in 2005 across all National Institute on Aging-sponsored Alzheimer's Disease Centers

11.4 TRAINING, CERTIFICATION, AND QUALITY CONTROL

<u>Cognitive Exam</u>

The field center lead examiner or study coordinator is responsible for the basic training of all new field center examiners. Training for new staff is listed below (very similar to training for ARIC/ACHIEVE examiners who had < 3 months of experience):

1. Careful study of the booklet/forms and QxQs for the MMSE, ESU, and NCS
2. Review of a training slide deck and successful completion of the associated content quiz (pass = 85%)
3. Review of training video demonstration and successful completion of the associated content quiz (pass = 85%)
4. Following the successful completion of items 1-3, examiners will obtain approval from the field center lead examiner or study coordinator and upload to the ARIC secure website 2 audio-taped neurocognitive assessments (performed on volunteers) along with copies of the associated paper protocols for review by Dr. Mosley or designated content experts at the University of Mississippi Medical Center

Training for previously certified ARIC or ACHIEVE examiners is based on previous neurocognitive testing experience. The general requirements for all experienced examiners includes:

1. Attend refresher training teleconference call,
2. Review neurocognitive booklet and booklet manual/QxQ
3. Review CDART forms (ESU, MMEO/MMEE, NCS)

Additional requirements for examiners with **less than 3 months** of testing experience:

1. Review NCG Training PowerPoint slides and pass corresponding test (85% +)
2. Review NCG Training Videos and pass corresponding test (85% +)
3. Practice and Role-play until proficient
4. Record/Upload 1 mock ppt for review (re-certification recording)

Additional requirements for examiners with **3+** months of testing experience:

1. Practice/role-play until proficient with battery administration and scoring
2. Optional: Review NCG Training PowerPoint slides and/or videos

Examiner certification for the neurocognitive exam is achieved by review and approval of performance by the neurocognitive expert.

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 and backup examiners, 2 times per month.

Neurologic Exam

Study staff are trained at a local field center 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, the CDR Training document, and discussion of challenges to data fidelity.)

Online training and certification for the CDR is required for new examiners (https://knightadrc.wustl.edu/cdr/Application/Step1.htm). Select 'This is my first time.' or 'I was trained more than 5 years ago.' for the full training. Experienced staff should use the above link and select 'I have received training with the last 5 years.' for the refresher training. The trainee should plan to review these videos over several days. When the staff member completes the online CDR training, the trainee will receive a completion certificate.

For new examiners or staff who last collected CDR more than 5 years ago, three audio-taped recordings of the CDR interviews (Informant and Subject interviews), the NHX, and NPI interviews and PDFs of associated documentation (NHX, NPI, CDR-informant, CDR-subject, and CDR-Summary forms) per trainee will be reviewed for certification. These sessions are ideally conducted with age-appropriate volunteers.

Training for new staff is listed below:

1. Complete online CDR training for new trainees https://knightadrc.wustl.edu/cdr/Application/Step1.htm
2. Review neurologic forms and corresponding QxQs (I.e., CDP, NHX, CDI, NPI, & CDS)
3. Review CDART forms (CDP, NHX, CDI, NPI, CDS)
4. Review the CDR Training document
5. Practice/Role-play with age-appropriate volunteers which should include at least one example of someone (real or fictitious, for the purposes of certification), with some cognitive complaints or problems until proficient with CDR administration and scoring
6. For certification, complete the training, then record/upload 2 mock ppt for review by the lead CDR reviewer and certifier, Tiffany Owens

Training for previously certified ARIC or ACHIEVE neurologic examiners is based on previous neurologic data collection experience. The general requirements for all experienced examiners include:

1. Attend refresher training teleconference call

1. Complete Refresher Modules on CDR Website (https://knightadrc.wustl.edu/cdr/Application/Step1.htm)
2. Review neurologic forms and corresponding QxQs (I.e., CDP, NHX, CDI, NPI, & CDS)
3. Review CDART forms (CDP, NHX, CDI, NPI, CDS)
4. Practice/Role-play until proficient with CDR administration and scoring

Additional requirements for examiners with **less than 3 months** of testing experience:

1. Record/Upload 1 mock ppt for review

Examiner certification for the neurologic exam is achieved by review and approval of performance by the lead CDR reviewer and certifier, Tiffany Owens.

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 and backup examiners, 2 times per month.

11.5 AUDIO-RECORDING OF NEUROCOGNITIVE AND NEUROLOGIC COMPONENTS OF INTERVIEW

Examiners are expected to record interviews, both cognitive and neurologic (CDI and NPI recorded from telephone or in-person), with the frequency defined in the table. Those examiners who collect cognitive and neurologic for both ARIC and ACHIEVE will only need to submit to one study or the other.

Number and Frequency of QC Neurocognitive and Neurologic Recordings to Upload	NEW EXAMINERS[1]	< 3 MONTHS[1]	3+ MONTHS[1]
Month on study	**Recordings to post**	**Recordings to post**	**Recordings to post**
1	2	2	1
2	2	1	
3	1	1	
4	1	None	
5+	1 every other month		

[1]The number of recordings to submit is based on prior experience with administering the in-person NCG battery. Months 5+ have the same requirements for all examiners.

All neurocognitive and neurologic QC uploads will be reviewed locally with a random sample to be reviewed centrally. Following a submission, email the local reviewer(s) that an audio recording has been uploaded to the website.

LOCAL REVIEWERS (A=ARIC, ACH=ACHIEVE)			
Forsyth	**Jackson**	**Minneapolis**	**Washington County**
Barb Anderson (A) Bria Backman (ACH) Josh Evans (ACH) Paula Riddle (A)	Rachel Foster (A, ACH) Tiffany Owens (A, ACH)	Sarah Aguilar (ACH) Nancy McCreary (A)	Jackie Bolinger (A, ACH) Amanda Miller (A, ACH)

Local reviewers: Please review the recordings within 1 week if possible. Email all QC feedback to Tiffany Owens (taowens@umc.edu). Following a completed review, please add your initials and the date to the QC recordings table on the ARIC or ACHIEVE website, then email arichelp@unc.edu to let the Coordinating Center know the review is complete. This will help the CC to keep the recordings table clear.

QC Uploading Schedule

Follow the QC uploading schedule below for uploading recordings for cognitive and neurologic exam. The examiner may upload recordings and files to the ACHIEVE Audio or the ARIC Audio if they collect data in both studies.

Recordings do not need to be collected according to the schedule. The assigned week is only relevant for the uploading.

Contact the QC reviewer (taowens@umc.edu for certification uploads; local reviewer(s) for recertification and QC uploads) when uploads are available. Include information in your email

about where the uploads may be found on the web site (ARIC or ACHIEVE). If you are unable to upload on a designated week please inform the QC reviewer as soon as possible.

1st Week of the month- Forsyth

2nd Week of the month- Jackson

3rd Week of the month- Minneapolis

4th Week of the month- Washington County

NCG and Neurologic Interview Components to be recorded and uploaded

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

Files to Upload[1]	NCG	Neurologic
AUDIO	1. ESU 2. MMSE 3. NCS Neurocognitive test battery	1. CDI (CDR-Informant) 2. NPI
PDF	1. NCS Neurocognitive test packet including loose materials (Trails, DSST, IL, MME pentagons)	1. CDS (if collected on paper before being entered into CDART)

[1]Neurocognitive reviews will include reviews of ESU, MMSE, neurocognitive battery, and the NCS. The reviewer will access the CDART forms directly in CDART; the CDART forms do not need to be uploaded to the Audio table on the website.

[1]The neurologic reviews will include reviews of the CDP, NHX, CDI, NPI, and CDS. The reviewer will access the CDART forms directly in CDART; these CDART forms do not need to be uploaded to the Audio table on the website.

11.6 INSTRUCTION FOR RECORDING INTERVIEWS

OLYMPUS DM-250 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 (Neurocognitive, Neurologic)
- Participant ID number
- Date
- For ACHIEVE only: Visit (e.g., baseline, YR 1, 2, or 3)

Step 5: Press **STOP** button on side of recorder to stop recording.

OLYMPUS TP-8 TELEPHONE PICK-UP MICROPHONE RECORDER

In order to record interviews that are completed over the phone (e.g., Telephone NCG battery, or CDI/NPI with an informant who was contacted by phone call), examiners will need the Olympus TP-8 pick-up device in order to record both parties on the phone.

Step 1: The examiner should wear a headset with the standard-type headband that goes over the ear instead of inside the ear (i.e., not earbuds)

Step 2: Plug the pick-up device into the recorder.

Step 3: Operate the recorder as instructed above. The pick-up device will record both your voice and the ppt/informant's voice on the other end of the phone call.

Step 4: When finished with the call, unplug the pick-up device and download your recording(s) as instructed below.

11.7 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	Participant ID	Date (YYYY/MM/DD)
M313_ M882731_2011-08-20_ Neurocog	M313_	M882731	2011-08-20
W429_ W892188_2011-08-20_ Neurologic	W429_	W892188	2011-08-20
J999_ J713456_2017-02-14_MMSE	J999_	J713456	2017-02-14

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.

11.8 INSTRUCTIONS FOR UPLOADING AUDIO FILES FOR REVIEW

The digital recordings are named following a standard naming convention: field center letter, staff ID, PPT ID, date (in YYYY-MM-DD format), and the interview component as described in the previous section and shown here: ***W406_W282829_2017-10-23_Component OR FORM CODES. Use Component name for audio recordings other than neurocognitive/neurologic. Use the FORM CODES in the naming when uploading neurocognitive/neurologic. For the special case when staff are uploading the neurocognitive recording and documents, where the recording includes all testing (ESU, MMSE, and neurocognitive) at the same time, the code 'neurocog' may be used in the filename. Similarly, when staff are uploading the NPI and CDI recordings with the paper CDS at the same time, the code 'neurologic' may be used.***

Step 1: Go to the secure area of the ARIC Study website. You will be asked for your username and password. All study personnel have access to the ARIC web site. Select Cohort → Audio from the menu on the left side of the screen.

Step 2: To initiate file upload, select the "Upload" button on the top right of the screen. For more detailed information on uploading files, click the "Instructions" button, located beside the "Upload" button. Click to open the PDF from the new tab.

Step 3: Enter information required by fields as follows:

a. Title: Enter any single character. This required field is a holdover from an earlier version of the grid and cannot be deleted.

b. Date: Enter the current date.

c. Field Center: Select from the list.

d. Recording Type: Select the recording type from the list.

e. Audio File Category: Select the relevant component.

f. Add a new file: Click 'Choose File' to browse for the audio file you want to upload, then select 'Upload' to complete the upload. Leave the Description box blank.

g. If necessary, upload additional, related documents by repeating step f. For example, upload the PDF of the Neurocog Booklet at the same time as the audio recording(s).

h. Information for reviewers: Use this text box to provide information about the files to the reviewers.

i. Review Date **(REVIEWERS ONLY)**: Select the "View · Edit" button under Review Date column. Reviewers enter initials to indicate that review is in progress. When the review is complete, enter the date of completed review to the field.

11.9 EXAMINER FEEDBACK

Examiners will receive feedback via written CERT or QC review and a follow up phone review when needed. Any errors/corrections that need to be made will show up as queries in CDART on the form with a correction/comment from the study participant ID who was recorded. The examiner will need to make corrections in CDART prior to the phone review. The QC reviewer will close the queries out on the phone review. Instructions for using the query system are found on the ARIC website listed as "Query System Users Guide" (https://sites.cscc.unc.edu/aric/training-cdart; Training>CDART).

12 Interviews

12.1 OVERVIEW

As in previous examinations of the ARIC cohort standardized questionnaires are administered by trained and certified interviewers who follow a common protocol. Standardization and adherence to protocol are particularly important considering that many of these interviews are intended to capture change over time by repeating questionnaires used previously by ARIC. While the cognitive battery interviews are always administered early in the visit , the remainder of the interviews can be administered in convenient blocks throughout the examination, or alternating with examinations to facilitate an efficient progression of the examination.

INTERVIEWS

12.2 MEDICATION SURVEY (MSR)

a. Rationale

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. This information assists in measuring patterns of medication use in the study communities, temporal changes in medical care practice, diagnostic classification of cardiovascular diseases, interpretation of laboratory results, and predictors of study end points.

The MSR and the Question-by-Question instructions for its use are found on the ARIC website. 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 in the CC).

b. Administration of the MSR

The MSR is divided into four major sections: A) Reception, B) Medication Record, C) Medication Use Interview, and D) Medication Adherence, administered as described below. To reduce the length of the visit it is important that staff complete section B, Medication Record, while the participant is occupied with interviews or procedures, and prior to completing section C and D (Medication Use and Medication Adherence Interviews). A further reason for staff to complete section C early during the visit is to make available the information on coded medications in the Data Management System, where – if applicable in the current visit –it can be interrogated by the ARIC technician for medications that exclude a participant from certain procedures (e.g., using a bronchodilator).

c. Reception

Trained and certified study personnel places identification labels on the participant's medication bag. Once the medication bag is logged and labeled, the interviewer checks with the participant to determine if it contains any medications that require refrigeration. Medications that require refrigeration are labeled with the participant's ID and placed in the refrigerator. The interviewer then determines and records whether the participant has brought in all medications taken within the last four weeks. If the participant has not brought in any (all) medications, the interviewer

inquires to differentiate between non-compliance with pre-visit instructions or non-use of medications in the prior four weeks. In case of inadvertent omissions, the interviewer makes arrangements for obtaining the information, preferably by having the participant return at a later date to the Field Center with the medications for scanning or transcription. The interviewer records deliberate omissions of medications on the MSR. Staff can administer subsequent parts of the MSR during Reception (if the work area affords the opportunity for maintaining confidentiality) or later, in an area designated for conducting interviews.

d. Medication Record

The interviewer first verifies that the name on the medication bag matches the participant's name. Then the interviewer removes all medication containers from the medication bag and places them on the work area. When there are more than 25 medications for scanning / transcription, staff uses the following algorithm to guide prioritization: [1] prescription medications; then [2] aspirin, aspirin-containing medications and anti-inflammatory drugs (see Question-by-Question instructions, List #1 and List #2); followed by [3] over-the-counter medications; and finally [4] vitamins, herbals, and supplements.

The interviewer scans / transcribes the UPC (part (a) of items 5-29) into the Data Management System. The Data Management System will try to match a Medical Therapeutic Classification (MTC) to the UPC. If MTC-UPC matching is successful, the Data Management System will skip the rest of the fields (parts b-d) for this medication item and move to the next medication. If an UPC is not available or the Data Management System does not successfully match the UPC, the interviewer transcribes the medication National Drug Code (NDC) (part a). If an NDC is not available or the Data Management System does not successfully match the NDC, the interviewer transcribes the medication name (part b), strength (part c) and units (part d).

If this is done in the presence of the study participant the interviewer shows each medication to the participant as it is scanned / transcribed, while keeping the other medications in view. The interviewer verifies scanned / transcribed information against container labels, making corrections when necessary to ensure accuracy. If a bar code label is not on the medication container or a bar code cannot be successfully scanned and a medication name exceeds the number of positions for the medication name (b) in the Data management System, the interviewer right-truncates the name without abbreviating the name in any other fashion. After successfully scanning / transcribing each medication, the interviewer returns corresponding containers to the medication bag to minimize confusion and to assure that all medications are returned to the participant.

Loose pills and medications in containers that are unmarked are examined only in the presence of the participant. With his/her permission and help, the interviewer examines loose pills and unclearly labeled containers, or those which hold more than one medication (e.g., medisets). The interviewer uses pill imprints, the Facts and Comparisons Drug Identifier on the desktop computer, and the Ident-A-Drug Reference on the web to identify these medications.

e. Medication Use Interview

The interviewer ascertains via a series of questions whether any of the participant-reported medications were used to treat pulmonary or cardiovascular diseases and/or their symptoms, whether any aspirin or aspirin-containing medications were used in the last four weeks, and whether any other non-steroidal anti-inflammatory drugs are being used on a regular basis.

f. Medication Adherence Interview

The interviewer ascertains via a series of questions if the participant is non-adherent with medications, the degree of non-adherence, and factors influencing non-adherence (e.g., method of payment).

g. Training and Certification

Interviewers are certified to administer the MSR after completing the following steps:

- The candidate is trained by a certified interviewer at the corresponding Field Center.
- The CC has sent to the Study Coordinator mock medications with detailed instructions for the candidate's certification.
- The candidate independently completes an MSR and enters it into the CDART2 certification system.
- The Study Coordinator informs the CC for evaluation. The candidate passes with a score of ≥ 80%.

h. Data Collection

The MSR is designed to be interviewer-administered and keyed directly into the Data Management System unless a workstation is not available. A paper version of the form is available for back-up and delayed data management. Medication UPC/NDCs (part (a) of items 5-29), medication names (part b), strengths (part c), and units (part d) should be listed alphabetically in hard copy. Details of data collection are provided in the Question-by-Question instructions for the MSR.

12.3 ALCOHOL USE FORM (ALC)

a. Rationale

The Alcohol Use Form is completed during the interview portion of the cohort visit examination, whether at the field center or in the course of a home exam visit. The questionnaire items correspond to those used in prior ARIC exam visits.

b. Administration

Frequency of alcohol consumption is determined as usual weekly intake, specifying the serving sizes for beer, wine and hard liquor. Also assessed are frequency in the past 24 hours, and the number of instances in the past 12 months where participants had more than 4 (females) or 5 (males) drinks within 2 hours. It is important that all interviewers be consistent in reading the questions clearly, and using the exact wording on the form, without omissions, additions or interpretations in reading the questions.

c. Training and Certification

Interviewers are trained and certified in general interviewing techniques and administration of this form. Staff can be trained centrally or locally at the field center. Retraining is required if quality assurance analyses indicate poor performance or inconsistent results.

12.4 CENTER FOR EPIDEMIOLOGIC STUDIES DEPRESSION SCALE (CESD) SHORT FORM

a. Rationale

Depressive symptoms have been linked to a number of important health outcomes including cardiovascular disease risk factors, CHD morbidity and mortality, cognitive functioning, and MCI/dementia. In ARIC-NCS visit examinations, depressive symptoms will be assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) Short Form (Kohout et. al, 1993). The CES-D Short Form is an 11-item questionnaire derived from the original 20-item CES-D (Radloff, 1977). In addition to a reduced administration time and clearer response options (relative to the 20-item version), the Short Form is highly correlated with the original ($r > .94$), has a high internal consistency, retains the same factor structure as the original, and has a similar positive predictive value as a screening tool for identifying clinical depression.

b. Administration

It takes approximately 3 minutes to complete this questionnaire. The questionnaire is administered by interview. The participant is provided with a response card listing the 3 response options. As a scale for depression, responses must be provided by the participant, not a proxy. Because of the sensitive nature of some of the questions, interviewers must take care to ask questions and record responses in a sensitive and non-judgmental manner. Most of the questions are self-explanatory; however, if the respondent is unclear, the interviewer will repeat the question and use general phrases, such as: “Answer as best you can, based on how you have felt over the past week.” Interviewers should not lead participants to an answer but remain neutral.

c. Scoring

Participants are asked to rate each item on a 3-point scale (scored 0 to 2) on the basis of “how often you have felt this way during the past week.” Response categories are:

- Hardly ever or never (scored as 0)
- Some of the time (scored as 1)
- Much or most of the time of (scored as 3)

CDART will compute a total score, calculated as the sum of the responses to questions 1-11. To control for response bias, questions # 5 and 8 are reverse scored. Scores range from 0 to 22 with higher scores indicating more severe depressive symptoms. If more than three items are missing, a score is not calculated. If one to three items are missing, scores on the completed items are summed; the total is divided by the number of items answered and multiplied by 11.

d. Training and Certification

Study coordinators are responsible for training new staff based on standardized interviewing techniques, QxQ instructions, and role playing example situations.

e. Depression Scores - Alert Guidelines and Notification of Participants and Physicians

The CES-D is not a diagnostic tool but may be used as a screening test to identify individuals at risk for clinical depression. In elderly participants, especially those with multiple comorbidities, some positive responses are expected.

A CES-D score ≥ 9 suggests probable Major Depression. Participants with scores in this range will be notified as well as their primary care physician by letter, indicating the presence of significant depressive symptoms on a common screening test and recommending a follow-up clinical assessment to evaluate for clinical depression and possible treatment. The alert letter is to be mailed within 2 weeks of receiving the CES-D results.

f. Procedures if Participants Report Depressive Symptoms Beyond Those Addressed in the Questionnaire (Off-the-Record) or Report Suicidal Thoughts:

During administration of screening tools such as the CESD, it is not uncommon for participants to reveal additional symptoms of depression. Participants who acknowledge significant depression should be advised to see their physician (psychiatrist or psychologist if they have one) within 48 hours so that an appropriate referral can be made.

Participants who acknowledge suicidal thoughts to interviewers should be referred immediately to the emergency room of the nearest hospital. If a participant refuses to go to the emergency room, he/she should be strongly encouraged to seek care as soon as possible. Staff should be aware however that no participant can be made to seek care against his/her will.

12.5 PHYSICAL ACTIVITY (PAC)

Information on habitual work and leisure-time related physical activity is collected by means of the questionnaire used in previous ARIC's visits, except for Visit 2 and Visit 4. Read each question aloud, including the specific activity type cues that pertain to each question. Then, read aloud the response options (Never to Always), including the descriptive prompts related to frequency of the activity that are provided for each response option.

At Visit 6, questions on physical activity within the household and transportation domain were added. Using #24 as an example, "Do you do the light household work, for example dusting, washing dishes, or repairing clothes? Would you say you do this "Never, or <1 time per month", "Sometimes or only when a partner or help is not available", "Mostly - sometimes assisted by partner or help", OR "Always - alone or together with help". Thus, participants provide responses via categories that are reflective of the frequency of activity and whether s/he engaged in that activity alone or with the help of another individual.

The Physical Activity (PAC) form and the instructions for its administration are found on the ARIC website.

a. Rationale

The assessment of physical activity in a cohort such as ARIC required that the instrument capture usual physical activity, be of known validity and reliability, and be as brief as possible. The ARIC Physical Activity questionnaire is based on a self-administered questionnaire

developed for a Dutch population by Baecke et al. (Am J Clin Nutr 1982;36:932-42). The questionnaire was adapted for ARIC and the same modifications and clarifications in the version translated from Dutch that were made in Visit 1 still apply.

Because older adults tend to engage in sports and leisure activities less in later life, the addition of questions regarding activities in the home and community provide supplemental information related to overall physical activity levels. This strategy optimizes the ability to appropriately rank participants' physical activity levels within the ARIC cohort.

b. Administration

The ARIC Physical Activity questionnaire is interviewer administered. Response cards are used to help the subject formulate a response. The interviewer introduces the questionnaire by reading the introduction given on the form. The interviewer then reads each question slowly, calling attention to the corresponding response screen for each question. The form, question-by-question instructions, and a physical activity coding dictionary are required.

For the additional questions to assess household and transportation-related physical activities, the interviewer also introduces the question by reading the instruction given on the form. Then, the interviewer reads each question slowly, including the specific activity type cues that pertain to each question. Then, the interviewer will read each response option (Never to Always) slowly, including the descriptive prompts related to frequency of the activity that are provided for each response option. Using #24 as an example, "Do you do the light household work, for example dusting, washing dishes, or repairing clothes? Would you say you do this "Never, or <1 time per month", "Sometimes or only when a partner or help is not available", "Mostly - sometimes assisted by partner or help", OR "Always - alone or together with help".

c. Coding and Scoring of Physical Activity

The coding of the physical activities reported by each participant is based on a physical activity dictionary which is appended to the QxQ instructions. The physical activities are coded by ARIC staff after the interview is complete (but not in the presence of the participant). Subsequent scoring of physical activity for purposes of analysis is done by the CC, based on the algorithm developed by Baecke et al. and Voorrips et al. (i.e., additional household and transportation related questions) (A physical activity questionnaire for the elderly. Med Sci Sports Exerc. 1991;23:974–979).

d. Training and Certification

Study coordinators are responsible for training new staff based on standardized interviewing techniques, QxQ instructions, and role playing example situations. Topics include proper coding of physical activities, usage of response cards, scoring and knowledge of when and how to probe.

e. Data Collection

The Physical Activity Questionnaire is administered by direct data entry in the DMS, with the help of response cards handed to the interviewee.

12.6 QUALITY CONTROL

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 may be used to monitor the quality of the data that interviewers collect as described below.

a. Certification on Interviewing Techniques

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

- Review 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.
- Study personnel certified on the interviewing techniques for a prior Visit are considered certified for the Visit immediately following.

Certification on interview techniques/survey instruments covers the procedures/techniques specified in Table 1 of the Certification Request Form.

b. Observation of Interviewing Technique

The supervisor will observe each interviewer (at least once) during the month following the interviewer's certification, or during the first month of a new examination cycle. The supervisor will rate the interviewer's performance using standard criteria from the Checklist for Observation of Interviewing Techniques (QC Appendix) and give the interviewer immediate feedback.

c. 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 survey training if one is scheduled, usually via webinar, or review of webinar training slides for local training.

Certification on interview techniques/survey instruments covers the procedures/techniques specified in Table 1 of the Certification Request Form available on the ARIC secure website [Cohort > Documents > select current visit].

12.7 QUALITY ASSURANCE

The data collected are periodically reviewed by the QCC from quality control analyses performed by the CC. In addition, automatic CDART queries are programmed to alert staff to out-of-range values and missing data. Monthly data quality reports will be prepared by the CC and reviewed by the QCC examining the frequency of out-of-range values, missing data, and summary statistics by field center.

13 Hearing

For specific procedure and training information about the hearing component, please refer to Manual 22 Audiometry.

14 Physical Function and Endurance

Physical function and endurance includes the physical function tests, Zeno gait mat measures, and the two minute walk. For specific procedure and training information about these components, please refer to Manual 32 Physical Function and Endurance.

14.1 PHYSICAL FUNCTION TESTS (PFX)

For specific procedure and training information about the physical function tests component, please refer to Manual 32 Physical Function and Endurance.

14.2 ZENO GAIT MAT (ZGM)

For specific procedure and training information about the Zeno gait mat component, please refer to Manual 32 Physical Function and Endurance.

14.3 TWO MINUTE WALK (TMW)

For specific procedure and training information about the two minute walk component, please refer to Manual 32 Physical Function and Endurance.

15 Accelerometry (ACC)

For specific procedure and training information about the accelerometry component, please refer to Manual 33 Accelerometry.

16 Ancillary Studies

The ARIC cohort examinations include core procedures and interviews that are administered to all examinees, primarily standardized to those used in prior examination visits. Sometimes included in ARIC's visit examinations are ancillary studies, approved by the ARIC Steering Committee and NHLBI staff and funded by various sponsors, selected based on their innovative study questions and scientific impact. To reduce study participant burden and for cost-efficiency, these ancillary study procedures may be integrated into the visit examination, administered by ARIC study personnel, harmonizing the participant safety provisions, data capture and management elements into a coherent, participant-friendly and efficient exam. This protocol manual describes this unified examination of the ARIC cohort member and makes reference to pertinent protocol manuals that are specific to each ancillary study and their detailed study procedures.

16.1 PYP SCAN

For specific procedure and training information about the PYP scan component, please refer to Manual 35 PYP Scan. In addition to the forms specific to PYP (PYRE, PYCD, PYPC), the PEX and RSX, both general ARIC forms, will also be collected. Training and Certification requirements for these forms are specified below.

a. Physical Exam Form (PEX) Training and Certification

Examiners are trained and certified by the chief trainer at each field center. Certification requires familiarity with the protocol and equipment, and successful performance of the two components of the physical examination on five volunteers, inclusive of data entry and transfer, witnessed by the trainer. After initial training and certification, re-training / re-certification may be required to maintain consistent quality.

b. Respiratory Symptom Questionnaire (RSX) Training and Certification

Interviewer supervisors are responsible for providing local staff training based on a common training manual, practice scripts, and role playing.

A certification by the supervisor or study coordinator is required and monitored by the Coordinating Center. Satisfactory performance on 5 observed (or recorded) interviews reviewed by the supervisor during the first month leads to certification. Recertification is not required.

16.2 CONTINUOUS GLUCOSE MONITORING

For specific procedure and training information about the Continuous Glucose Monitoring component, please refer to Manual 39 Continuous Glucose Monitoring.

17 Data Inventory

A data inventory is done after all interviews and examination procedures have been completed and prior to the Exit Interview. Because participant data are collected by various means during the course of the exam, the objective of this inventory is to verify that all data items have been collected before the participant leaves the study center.

The CDART form grid serves as the visual inventory of forms that have been entered into the system. Forms that have not been entered will have a blank ‘Form Status’ on the form grid. A non-missing form status is in no way intended to indicate complete data collection of a form. Updating the form status is left up to the discretion of the field center and is intended to serve as a visual aid in detecting inadvertently missed forms. Refer to the CDART tutorial for instructions on how to update form status.

18 Exit Interview

The end of visit debriefing provides an opportunity to ask for feed-back about the visit and to identify aspects that the participant may have perceived as stressful or unpleasant. It also provides an opportunity to re-establish rapport with the study participant and to seek commitment for a long-term association with the ARIC study. The participant is reminded of the six-month follow-up call, and at the field center's discretion the call can be scheduled at that time.

The summary of results provided at the end of the examination visit is discussed with the participant, and any results identified at this time for confirmation or referral for medical care are discussed. The participant is told that a written summary report, including additional tests, will be mailed to the participant and his/her physician (or alternate) six to eight weeks after the field center exam. It is important to establish who is authorized to receive the report of study results, according to the participant's instructions. If a proxy provided informed consent on behalf of the study participant, it is the proxy who should receive the participant's study results. In this process, staff must be sensitive to the participant's self-esteem; if authorized by the proxy, ARIC staff may provide of the study results to the study participant.

During the administration of the CES-D or during the Exit Interview a participant may reveal indications of depression. Participants who acknowledge significant depression should be advised to see their physician (psychiatrist or psychologist if they have one) within 48 hours so that an appropriate referral can be made. If in doubt whether a referral is needed, ARIC staff conducting the exit interview must consult with their supervisor or the study coordinator. A list of referral services available in the ARIC study community is kept on file.

Participants who acknowledge suicidal thoughts to interviewers should be referred immediately to the emergency room of the nearest hospital. If a participant refuses to go to the emergency room, he/she should be strongly encouraged to seek care as soon as possible since no participant can be made to seek care against his/her will. This requires consultation with the study coordinator and/or the medical professional on call for the ARIC field center. Once the participant has been placed in the care of a health service or qualified professional, an adverse event form is filed.

19 Participant Safety

The safety of the ARIC participants is protected by specific measures taken in the design or conduct of the examination for their safety; by the procedures in place for handling potential emergencies; the routine notification of participants and their physicians regarding the results of the examination, and procedures used to alert participants and their physicians of results deemed to have potential medical importance according to established clinical guidelines.

For participant safety reasons the use of a pacemaker or defibrillator and a physician diagnosis of diabetes are ascertained at the time of scheduling the exam visit and confirmed on arrival the ARIC field center. The master record used in ARIC to document and monitor safety is the PSA Form, which serves as the summary record of safety items in the ARIC database and is the register by which the study monitors compliance with the safety protocol. Thus, if the study participant or an authorized ARIC staff person updates safety information provided previously the PSA form must be updated. This is done by (a) changing the pertinent response on the PSA in CDART, and (b) by adding a note log to that item with a brief explanation for this action and the staff person's ARIC ID.

19.1 MEASURES TO PROTECT THE PARTICIPANT

Examination procedures which convey potential – although small – risk to participants include the phlebotomy (not conducted at every visit) and the measurement of bioimpedance. Precautions are taken to minimize the risk associated with these procedures, and any risks potentially related to morbidity or traits of the study participant, as detailed below. At the time a participant's ARIC examination is scheduled conditions or circumstances that may convey risk in the course of the ARIC examination are ascertained and recorded and may result in exclusions from a test or measurement. Medical conditions, food allergies or dietary restrictions which may be incompatible with the snack provided by the field center are also ascertained. The PSA form must be completed before a participant can proceed through the ARIC examination. The form is completed in CDART and copy can be printed if is to accompany the ARIC participant throughout the course of the examination. Alternatively, the Field Center may use the Visit Exam Checklist (Appendix 2), which includes the safety information from the PSA form and accompanies the participant throughout the field center examination.

Verification of a safety exclusion for phlebotomy or the use of the bioimpedance feature on the Tanita scale is the responsibility of the technician performing the procedure. ARIC staff may re-ask the pertinent safety exclusion question, and may confirm with the study participant an exclusionary condition noted on the PSA form (as Yes). If the condition is deemed to have been recorded in error, the technician may override the previously recorded response/exclusion if authorized to do so. Otherwise the technician asks for input of a supervisor.

The ARIC staff person conducting the Exit Interview reviews the procedures performed and verifies the agreement with the exclusion conditions noted on the PSA form or the Visit Exam Checklist. Any discrepancies between exclusion conditions recorded on the PSA form and a test performed are reviewed with the Study Coordinator, the Study Physician or Nurse. The participant's wellbeing and safety must be addressed before the participant leaves the premises.

Participants may experience syncope during the venipuncture (not conducted at every visit). Hematomas or prolonged bleeding resulting from venipuncture are usually avoided if well-trained technicians follow the procedures for blood drawing and take the precautions described in ARIC Manual 7. Occasionally, bleeding persists after Venipuncture, in which case procedures described in Manual 7 are followed. Methods for handling major and minor emergencies are described below.

For persons with conditions which require emergency and immediate referrals, such as cardiac events, angina pain, or blood pressures $\geq$ 200/120 mm Hg (see Section 20.4), the ARIC clinician is consulted immediately, the clinic exam is terminated as soon as the condition is observed, and another appointment rescheduled if appropriate.

19.2 PROCEDURES FOR HANDLING EMERGENCIES

While all life threatening emergencies (e.g., acute MI) require immediate evaluation of the participant at an acute care facility, some emergency measures may be required in the clinic before departure. In addition, there are minor emergencies (hypotension, fainting, etc.) which need to be addressed on the premises. Although most emergencies are of the less severe nature, ARIC field centers must be prepared for both types.

19.3 MAJOR EMERGENCIES

In a serious event the primary concern of the clinic staff is to address the participant's safety and implement pre-established procedures to get the participant to the nearest medical facility. All ARIC centers are located within a few city blocks of a large, general, acute-care hospital. A staff person with certification in basic life support must physically present at every exam session. Needed life support procedures are continued until emergency care arrives or the participant is transported to a hospital. Each ARIC field center, depending on its location and staffing patterns, has specific emergency procedures, which define:

1. Who is in charge during the emergency.
2. Who is to administer treatments.
3. Who is to be notified.
4. What action clinic staff is to take.
5. Which reports are to be filed.

Each field center is required to have access to either a physician, a physician assistant or a registered nurse at all times during which participants are interviewed and examined. In addition to trained personnel and emergency equipment, each field center has the following information posted in conspicuous places: phone numbers of police and fire stations; ambulance services; and specific phone numbers or codes to alert medical teams, if applicable. The name and phone number of the participant's physician or usual source of health care and the home and work telephone numbers of one or more contact persons should be available in each participant's record.

Emergency situations are coordinated by the staff person designated a priori, or by a physician if present. Each center has a designated physician on call. If not physically present in in the field center, he or she is within immediate reach by phone or paging system. The physician roster is

posted in the field center and in the office of the nurse/clinician so that the name of the responsible physician is readily accessible. However, in no case is an emergency referral and/or care to be deferred while staff is attempting to locate the designated ARIC physician.

All emergencies, whether serious or minor, are documented. This requires filling out an institutionally-approved form identifying the type of emergency. This is done by the person in charge at the time, co-signed by the designated nurse or physician and are filed at each center.

19.4 MINOR EMERGENCIES

The most common minor emergency is simple syncope (fainting) and near syncope. These events may occur during venipuncture. The management of simple syncope or near syncope follows the procedures detailed in Manual 7.

Many syncopal episodes can be prevented if clinic staff is alert to early signs. In any situation in which syncope is likely, e.g., after the venipuncture or standing up after s supine examination procedure, staff stands close to the participant and verifies that he/she does not look or feel faint. If the participant looks faint or feels faint in the venipuncture area:

1. Have the person remain in the chair and sit with head between the knees or recline if the appropriate chair is used at the field center.
2. Crush an ampule of smelling salts and wave it under the participant's nose for a few seconds;
3. Provide the participant with a basin and a towel if he/she feels nauseous;
4. Have the participant stay in the chair until he/she feels better and color returns.

If the participant continues to feel sick, recline the chair, place a cold wet towel on the back of the person's neck, and notify the supervisor. If a participant faints, he/she is cautiously lowered to the supine position on the floor and one attendant immediately calls for an in-house nurse/clinician to assist the patient. The remaining attendant raises the patient's legs above the plane of the body to increase venous return. Prior to this, the staff member momentarily palpates for a carotid pulse and checks to be sure the subject is breathing.

Hypoglycemia (blood glucose < 50 mg/dL with or without symptoms) refers to an abnormally low blood glucose level and can occur during fasting or as an imbalance between the dose of hypoglycemic medications and the person's food intake and activity level. Symptoms of hypoglycemia associated with blood glucose in the range of 30-50 mg/dL are not very prominent in persons without diabetes. The most common are hunger, yawning, and a mild headache. Symptoms associated with blood glucose lower than 30 mg/dL may include irritability, pallor and cold sweat.

Individuals with diabetes who experience hypoglycemia may complain of headache, blurred vision, tingling around the mouth or tongue, tachycardia, sleepiness, weakness, feeling unable to concentrate or articulate words, nausea and dizziness. Physical signs of hypoglycemia range from cold sweat, shaking, slurred speech, incoherent thoughts, and syncope. Persons with a history of poorly controlled diabetes, or Type 1 diabetes may not manifest symptoms or signs of hypoglycemia but suddenly pass out. Some may have visible sweat and pallor, yet indicate that they feel fine.

Prolonged hypoglycemia may precipitate angina pectoris or seizures. *It is important to remember that symptoms of hypoglycemia are variable and may be partially masked in older participants.*

If a person displays any of these symptoms and is able to take food orally, 8oz of orange juice should be given immediately and the clinic nurse or physician notified as soon as possible. If a hypoglycemic reaction has occurred the person is evaluated by clinical staff prior to leaving the field center.

Severe hypoglycemic reactions are a medical emergency that requires transport to an emergency care facility. Should a participant with hypoglycemia become stuporous or non-responsive, oral replacement with glucose should not be administered in order to avoid aspiration (intramuscular glucagon or intravenous dextrose should be administered, for which the participant needs to be immediately transferred to the nearest emergency room (ER)). Oral glucose gel can be placed on the inside of the cheeks, while transfer to an ER is arranged.

19.5 EMERGENCY EQUIPMENT

A basic first aid kit is maintained at each field center. The kit contains a reference guide of its contents, and is checked every year and immediately after each use. At each field center the Study Coordinator identifies a person responsible for its maintenance.

19.6 PROCEDURES TO DEFINE AND REPORT ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

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 timelines (http://www.hhs.gov/ohrp/policy/advevntguid.html).

19.7 ADVERSE EVENTS AND UNANTICIPATED PROBLEMS - DEFINITION AND REPORTING IN ARIC

Per OHRP guidelines we define an adverse event as an adverse change in health or unfavorable medical occurrence that occurs in a person who participates in ARIC, which may or may not be caused by participation in the study. Adverse events include both physical and psychological harms, temporally associated with the individual's participation in the research, whether or not considered related to the subject's participation in the research. Pre-existing conditions detected as a result of participation in ARIC, its tests and examination protocols do not by themselves constitute an adverse event. Adverse events and problems that are not foreseen or mentioned in the study protocol or the informed consent are considered unanticipated. If an unanticipated problem suggests that the research places the participant at increased risk (as defined below) the unanticipated problem must be reported to the local Institutional Review Board (IRB), and to the study sponsor (NHLBI) as described below.

Adverse events and unanticipated problems must be addressed promptly according to institutional safety guidelines and the ARIC study protocol, to quickly resolve any safety concerns or participant discomfort. The supervisor, medical director and/or principal investigator

are notified according to the perceived severity of the event and the event's perceived relation to participation in the study.

19.8 DEFINITION AND CLASSIFICATION OF AES IN ARIC

a. Serious (as Opposed to Minor or Non-Serious)

An adverse event is serious (SAE) if it affected a pregnant study participant, a fetus or a newborn, or if it results in any of the following outcomes:

1. Death
2. A threat to life
3. Requires (inpatient) hospitalization, operationally defined as 24 hours or more
4. Likely causes persistent or significant disability or incapacity
5. Likely associated with a congenital anomaly or birth defect
6. Requires treatment to prevent one of the outcomes listed above, other than for pre-existing conditions detected as a result of participation in ARIC, its tests and examination protocol.

b. Expected (vs. Unexpected) AEs

An adverse event is unexpected if the risk information is not mentioned in the consent form, if the AE is not mentioned in the study protocol, or if the AE is not reasonably expected to be related to study procedures. The study procedures in ARIC are deemed to be safe. Serious adverse events (SAEs) are therefore unanticipated and unexpected, whether study related or otherwise.

c. Study-Related, Possibly Study-Related, or Not Study-Related

- Related AE – An adverse event which is related to the use of a device, procedure or an ingested substance in a way that supports a reasonable possibility (such as strong temporal relationship) that the adverse event may have been caused by the device, procedure or intervention used in ARIC.
- Possibly Related AE – An adverse event which is possibly study-related is one that may have been caused by a procedure, device, or ingested substance, with insufficient information to determine the likelihood of this possibility.
- Unrelated AE **–** An adverse event that has no apparent relationship to the study.

It can be difficult to determine with certainty whether a particular AE is related or possibly related to participation in research. This often requires an assessment of how likely an AE is related to participation in ARIC, ranging from definitely related to definitely unrelated, classified into one of three options shown above. Many of the AEs that occur in the course of participation in a study such as ARIC are not related to the research procedures or the setting the research takes place in.

19.9 DEFINITION AND CLASSIFICATION OF UNANTICIPATED PROBLEMS (UPS) IN ARIC

OHRP considers unanticipated problems to include any incident, experience, or outcome that meets ALL of the following criteria:

1. Unexpected;
2. Related or possibly related to participation in the research; and
3. Suggesting that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The large majority of adverse events are unanticipated. Unanticipated problems can include unforeseen incidents, experiences or outcomes; if they also are related or possibly related to participation in ARIC and indicate that they place the study participant or others at a greater risk of harm they qualify as a UP and ARIC personnel must act on them as described below.

All serious adverse events (SAEs) are considered to be unanticipated and unexpected, whether they are study-related, possibly study-related, or not study-related. In contrast, not all unanticipated problems (UPs) are SAEs.

19.10 REPORTING OF ADVERSE EVENTS AND INFORMATION FLOW

If a study participant experiences an adverse event or unanticipated problem, the first priority for ARIC staff is to attend to the participant's safety. While a staff person always remains with the participant, the field center medical staff is notified, and if warranted, 911 is called. Once the participant's safety and comfort have been addressed and the situation is not considered emergent, reports are prepared to notify the Institutional Review Board (IRB) according to each IRB's guidelines, and all AEs and UPs are promptly recorded in the CDART. Events are recorded in CDART using the pertinent form for a Serious Adverse Event (SAE), a Minor (not serious) Adverse Event (MAE), or an Unanticipated Problem (using the UPR form). Each time a SAE or UP is entered in CDART the ARIC staff person completing this task should promptly notify Arichelp by email that such a form has been entered.

Completion of a SAE, UPR, or MAE form in CDART results in a review of the report by the ARIC CC and a report of the event to the NHLBI according to schedules shown in Table 19.1. No direct notification of an adverse event or UP to NHLBI is required of the field center. Adverse events not considered serious and anticipated problems are summarized periodically by the CC for the NHLBI, the OSMB, and the Steering Committee. The reporting schedule of AEs and UPs in ARIC is presented in Table 19.1.

19.11 TRAINING AND CERTIFICATION

To be certified, staff must be familiar with sections 19.6-19.10 of this manual, and the Serious Adverse Event (SAE), Minor Adverse Event (MAE), and the Unanticipated Problem (UPR) forms and their QxQs. For certification purposes, the ARIC Visit calibration set for adverse events and unanticipated problems (QC Appendices) should be completed for review by the study

coordinator. A staff member certified in this task during a prior ARIC Visit is considered certified for the Visit immediately following, and can train and certify other staff at the field center.

Table 19.1. Types of unanticipated problems and adverse events, and required actions by the ARIC Staff and Timing

	ARIC Field Center			**Coordinating Center**	**ARIC Operations Committee**	**ARIC Steering Committee**
1) Unanticipated Problem (UP)						
Response	Address any ppt. safety issues; inform medical director and PI	Record UP in ARIC DMS (CDART), notify Arichelp	Report UP to IRB	Notify NHLBI via the CC	Review study procedures; propose revisions if warranted	Review report of AE and study procedures; modify protocol if required
Time / Schedule	Immediate	48 hrs	72 hrs	Within 7 calendar days	Within 14 calendar days	Within 30 calendar days
2) Serious Adverse Event (SAE)						
Response	Address any ppt. safety issues; inform medical director and PI	Record SAE in ARIC DMS (CDART), notify Arichelp	Report SAE to IRB	Notify NHLBI via the CC	Review study procedures; propose revisions if warranted	Review report of AE and study procedures; modify protocol if required
Time / Schedule	Immediate	48 hrs.	72 hrs.	Within 7 calendar days	Within 14 calendar days	Within 30 calendar days
3) Minor Adverse Event (MAE)						
Response	Address any ppt. safety / comfort issues	Record AE in the ARIC DMS (CDART)	Report AE to IRB	Notify NHLBI via the CC	Review study procedures with experts; propose revisions if required	Review report of AE and study procedures; modify protocol if required
Time / Schedule	Immediate	7 days	Within 7 calendar days	Quarterly	Within 30 calendar days	Quarterly
4) Anticipated Problem, not an AE						
Response	Address any ppt. comfort issues	Not reported (not recorded in CDART)	Report to IRB not required per OHR	Report to NHLBI not required	N.A.	N.A.

	ARIC Field Center			Coordinating Center	ARIC Operations Committee	ARIC Steering Committee
Time / Schedule	Immediate	N.A.	N.A.	N.A.	N.A.	N.A.

19.12 SAFETY EXCLUSIONS FROM STUDY PROCEDURES

a. Exclusion from Any Study Component

SBP >=200 or DBP >120 mmHg (Stop exam visit, arrange for urgent care)

b. Exclusion from Bioimpedance Estimation

Cardiac pacemakers (or automatic implanted cardiac defibrillator (AICD), if in doubt)

c. Exclusions from the Two Minute Walk

The participant is not able to complete the 4-meter walk without a walking aid; the participant has a resting heart rate of 110 bpm or greater; the participant has a systolic blood pressure >180 mmHg; or the participant has a cast or other immobilizing device on a leg

d. Exclusions from the 4-meter walk

The participant has a cast or other immobilizing device on a leg

See Manuals 35 (PYP) and 39 (CGM) for ancillary study specific exclusions.

19.13 REFERRAL FOR MEDICAL CARE

A need to refer the study participant for care by a health professional may arise from several circumstances or study results encountered during an examination visit. As noted in Section 19.3, life threatening emergencies require immediate evaluation of the participant at an acute care facility whereas minor emergencies (hypotension, fainting, etc.) are typically addressed on the premises.

An elevated blood pressure that exceeds ARIC's safety thresholds is a relatively frequent reason for referral to medical care. The urgency or timeliness of the referral is determined by the observed blood pressure level:

1. A sitting, average SBP >=200 or DBP >120 mmHg requires ARIC personnel to stop the exam visit and arrange for urgent care. This may be at an emergency department or a confirmed, same day appointment with the study participant's usual provider of medical care. The urgent need to evaluate and act on this degree of blood elevation is explained to the study participant, and ARIC personnel assist in arranging for the referral.
2. A sitting, average SBP of 180-199 or DBP 110-119 mmHg prompts a referral for medical care within 48 hours. The examination visit may proceed. ARIC personnel explain the need for a prompt evaluation and blood pressure-lowering by a medical professional, and assist in making an appointment within 48 hours. This may be with the participant's usual provider of medical care.

19.14 STOPPING RULES FOR INTERVIEWS AND PROCEDURES

a. Fatigue/Discomfort

Interviewers and technicians observe participants for signs of fatigue or physical and/or emotional discomfort. When any one of these conditions are observed, participants are offered the opportunity to discontinue the interview or procedure, and are given an opportunity to rest before being taken to the next work station. If in the course of the field center visit a participant seems to exhibit anxiety when instructed to perform tasks or shows a pattern of repetition or empty responses during interviews and/or seeks assistance from others during interviews, the staff person uses a break between procedures to bring this to the attention of the supervisor. The supervisor can decide whether the participant should be asked to complete the longer interviews that remain on the participant's schedule. Persons incapable of completing the full field center exam are invited to participate in the exit review and complete the remainder of the exam on another day (either at the clinic, or via a home visit).

b. Mental Health Emergency Procedures

In the course of the ARIC field center activities there are a number of circumstances that require training and judgment on the part of staff, consultation regarding clinical decision making, and filing of incident reports. They include medical emergencies, participants who may be suicidal, participants who may be homicidal, participants who appear intoxicated, indications that it may be necessary to file a child abuse report, and circumstances when it may be necessary to file an elder or dependent adult abuse report.

While several of these situations will not be directly assessed in ARIC, procedures are in place at the ARIC field center for the eventuality that any of these issues arise during the course of the study. Each of these instances must be handled with caution and sensitivity, in a way that ensures that the appropriate clinical decisions are made. Information regarding each of these separate circumstances is presented below.

ARIC field centers have personnel trained to respond to physical and medical emergencies, and certified according to their institutional policies. As mentioned above, contact and locator information for medical emergencies and physical threats are displayed throughout the field center. In all emergencies and crises study personnel contact the supervisor, consultant or security personnel according to the circumstances. If the situation is associated with potential harm to a study participant, action is taken and resolved prior to the participant's departure from the premises. An incident report is filed and documented within 24 hours of an incident in order to provide a record of the actions taken by the staff and supervisors. The study principal investigator is informed of the incident and of any action taken by the study personnel.

c. Participant Appears Intoxicated

Participants who arrive at the field center potentially intoxicated are asked not to participate in the research procedures at that time. The clinic manager is notified of any suspicion of intoxication. The interviewer or clinician will explain to the participant why he or she will be excluded from the procedures and why s/he should leave the research premises (i.e., that s/he appears to be intoxicated, smells like alcohol, is staggering). To protect the participant from possible injury, interviewers and/or clinicians must make sure that she/he does not drive home, either by calling a taxi or calling the police to escort him/her home.

20 Report of Study Results, Medical Referrals and Notifications

To serve its study participants and the community ARIC returns study results that have potential clinical value. Study results that have established value for medical diagnosis or treatment are reported to the study participants by following current guidelines for care endorsed by professional societies and governmental agencies. Laboratory tests and examinations performed by ARIC that are of research value only and not directly relevant in the context of current guidelines are not reported to avoid burden to the study participants and their medical practitioners. As part of the informed consent process, study participants are told that they are taking part in a research study that follows a research protocol. They are also informed that procedures are not identical to those performed in a regular clinical examination, and that they will only receive study results that are of known value to medical practitioners.

Information on examination and laboratory test results are shared with ARIC participants during an interview at the end of their field center examination visit, and subsequently (at visits when biospecimens are collected) once test results are returned by the ARIC central laboratory and reading centers responsible for standardized processing of the data. The reporting schedule incorporated into this process is a function of alert ranges that define emergent, urgent or routine notification. This process is described below.

20.1 PROCEDURES FOR MEDICAL REFERRALS AND NOTIFICATION OF RESULTS

Since the participant's safety is of paramount concern, data collected during the examination that could indicate the need for referral for medical care are reviewed with the participant prior to the completion of the examination, during the exit interview unless the alert condition required stopping the examination. The type of study result to be reported to the study participant and the schedule of notification also are reviewed at this time. An additional purpose of the exit interview is to verify that all components of the field center clinic visit have been completed, to solicit comments and feed-back from the participant, to return the participant’s medications, and answer any remaining questions. Values or measurement results that exceed the thresholds underwritten by treatment guidelines are identified to the participant with a recommendation for review and or confirmation with their provider of medical care. The study defines these notifications as a referral, although such notifications emphasize to the study participant and his/her provider of care that the results originate from a research protocol and cannot be equated to a clinical evaluation.

20.2 MEDICALLY RELEVANT INFORMATION

Medically relevant information is provided to the study participants and their providers of medical care, if so authorized by the study participant. If consent to provide this information to the person's physician was given as part of the informed consent process, copies of the reports of study results are sent to the participant's physician. With the exception of a proxy designated by the study participant no study information is shared with other persons or entities, other than with the written authorization of the participant, or as required by law.

Clinically relevant values in the study data that are so abnormal as to be considered an "alert value" according to the threshold levels listed in Table 20.2 trigger a rapid notification process as described below. Study results that exceed the study guidelines but do not meet “alert”

threshold criteria are identified to the study participant for a consultation with their provider of medical care, for confirmation. Lastly, measurements and assay results that are within normal ranges according to the guidelines in use in ARIC are reported in a consolidated summary report to the participant once all information has converged to the collaborative database. This report includes any results previously reported to the study participant on an expedited schedule ("alert values").

Medical information is provided to participants (and physicians) is thus provided at the following points:

1) Exit Interview. During the exit interview at the conclusion of the field center examination, a staff member gives the participant a "clinic visit report" and reviews their weight, estimated body fat if desired, current blood pressure, and audiometry test results. The "clinic visit report" also indicates to participants that they will receive by mail a copy of the interpretation of selected blood tests and feedback on their meaning.

2) Alert Notifications. Measurement values and incidental findings designated as alert values can be detected at the ARIC field center or in the course of an MRI exam. Definitions of alert conditions are set out in Table 20.2. Study data processed by the ARIC central laboratories and the ARIC reading centers are transmitted on an ongoing basis to the CC, where they are screened upon receipt for alert values and processed for preparation of study results reporting. From the ARIC central database, field centers can interrogate the data any time via the CDART to generate an Alert Notification Report. Each ARIC field center designates one staff person and his/her back-up to generate a daily report of study results to be reported as alert values received by the ARIC CC during the previous 24 hours. Field centers can generate reports of alert values by exam date or by ID.

For notifications of alert values to ARIC study participants or their proxy, and/or the provider of care designated by the participant field center personnel print and send a personalized Participant Alert Letter (see Appendix 3 and/or a Physician Alert Letter (if permission was obtained to release these data to a physician). Phone calls may be placed to the study participant, a proxy or a provider of medical care if warranted by the severity of the suspected condition notified.

3) Summary of Results. Once all results from the central laboratories and the central reading centers are received at the CC or after 8 weeks since the participant's examination visit have elapsed, the Summary of Results is assembled by the respective field center as a report feature in CDART. This report lists the individual study results of medical value, a scripted interpretation corresponding to the value or finding reported, and an indication whether follow-up with a medical practitioner is recommended for a given result, with the recommended time frame for the follow-up. ARIC field center personnel prepare personalized cover letters to the study participants and their physician (if permission was obtained to release these data). The cover letter highlights any noteworthy results for the study participant. Field center personnel are encouraged to place these results in context of a participant's known medical history before reporting such results, and consult with a field center's medical director as needed.

20.3 QUALITY ASSURANCE

Actions taken in response to an alert value are documented on the Results and Alert Reporting form. The occurrence of an alert condition and its processing from the originating laboratory or reading center to the notification of a study participant and/or the physician is journaled by the data management system maintained by the CC. The timeliness of this process and its successful completion according to study protocol are included in the quality analyses performed by the CC and are periodically reviewed by the QCC.

20.4 ACTIONABLE STUDY RESULTS

a. Seated Blood Pressure

Three measurements of seated blood pressure are recorded with an OMRON HEM-907XL IntelliSense® digital blood pressure monitor, after a five-minute rest period. The averaged value of the three measurements is reported to the study participant during the exit interview. The blood pressure measurements and the actions to be taken are reviewed according the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines (Whelton PK et al, Hypertension, 2017). This information is summarized in Table 20.1, below. These guidelines are used by ARIC personnel in communications with the study participant and in making follow-up recommendations unless/until new clinical guidelines are released. Table 20.2 provides an overview of study results reported to the ARIC study participants, the corresponding threshold values and the explanatory scripts.

Table 20.1. Classification of Blood Pressure in ARIC, according to the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults*

Blood Pressure Category	Systolic Blood Pressure		Diastolic Blood Pressure
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120-129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130-139 mm Hg	or	80-89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

SBP= systolic blood pressure. DBP= diastolic blood pressure.

* Source: Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/ AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017;

The 2017 Guideline states that blood pressure classifications and referral recommendations should be based on an average of 2 or more careful readings obtained on two or more occasions. ARIC uses the average of 3 blood pressure readings in order to reduce the impact of

reactivity (first readings are usually higher) on the estimate of the value of the underlying blood pressure. Individuals with SBP and DBP in different categories should be designated to the higher BP category.

b. Blood Chemistry Measurements

Phlebotomy does not take place at all ARIC visits. For visits when phlebotomy occurs, laboratory assays are performed at the ARIC Central laboratories at Baylor University or the University of Minnesota, which also maintain the ARIC biospecimen repositories. Assays with actionable results performed at the visit and the reference and alert values used by the ARIC central laboratories are summarized in Table 20.2. Other assays performed on visit specimens are of research value only.

Table 20.2 Criteria for emergent and urgent notification from Visit 9 assessments. Threshold values for results reported as normal, abnormal, or alerts and interpretations included in the report to study participants/their provider of health care

Measurement	Threshold Values / Trigger conditions	Reported to participant as:			Script for Report
Seated blood pressure	SBP <120 and DBP <80	Normal			Your blood pressure was normal. Please recheck it in one year. If you are being treated for high blood pressure, your physician may have given you a schedule for your next check-up. Please follow that schedule.
Seated blood pressure	SBP 120-129 and DBP <80	Normal			Your blood pressure was somewhat elevated, according to recent guidelines. Please recheck it in 3-6 months. If you are being treated for high blood pressure, your physician may have given you a schedule for your next check-up. Please follow that schedule.
Seated blood pressure	SBP 130-139 or DBP 80-89		Abnormal		Your blood pressure was high, according to recent guidelines. You should have your blood pressure checked within two months by a physician. If you are being treated for high blood pressure please see your physician.
Seated blood pressure	SBP 140-179 or DBP 90-119		Abnormal		Your blood pressure was quite high. You should have your blood pressure checked within a month by a physician. If you are being treated for high blood pressure, please see your physician.
Seated blood pressure	SBP 180-199 or DBP 110-119			Alert Arrange for medical evaluation within 48 hrs	Your blood pressure was very high. At the time of your ARIC visit we indicated that you should see a medical professional within 48 hours to determine whether treatment should be started or changed. If you have not done so already, please see your physician without delay.
Seated blood pressure	SBP >= 200 or DBP >=120			Alert. Stop the exam & arrange for same-day eval.	Your reading was very high. At the time of your ARIC visit we indicated that you should see a medical professional within hours to determine whether treatment should be started or changed. If you have not done so already, please see your physician without delay.
Weight	Value	Can use ‘Normal’ cover letter			N/A

Measurement	Threshold Values / Trigger conditions	Reported to participant as:			Script for Report
Body mass index (BMI)	N/A	Can use 'Normal' cover letter			The body mass index (BMI) is an estimate of your body fat, based on your height and weight. In adults, the BMI provides information on health and potential health risks. A BMI of less than 18.5 is Underweight; 18.5 to 24.9 is Healthy; 25.0 to 29.9 is Overweight; 30.0 or more indicates Obesity
Depression finding	CES Form Q13 (sum) >= 9			Alert	At the time of the ARIC examination we provided a letter recommending review of possible depression by a health professional
Triglycerides	Triglycerides >=1000 mg/dl			Alert (only in Results Report)	Non-Fasting: Your serum triglyceride is very high. You should check with your physician about this as soon as possible. Serum triglyceride was measured from a non-fasting sample and should be repeated with a fasting sample. Fasting: Your serum triglyceride is very high. You should check with your physician about this as soon as possible.
Total cholesterol	Value	Can use 'Normal' cover letter			Total cholesterol levels less than 200 mg/dL are optimal.
HDL-cholesterol	Value	Can use 'Normal' cover letter			HDL-cholesterol values below 40 mg/dL are sub-optimal.
Calculated non-HDL-C	Value	Can use 'Normal' cover letter			Non-HDL cholesterol values above 150 mg/dL are suboptimal.
Hemoglobin	Female: 11.7 - 15.7; Male: 13.3 - 17.7	Normal			For women, hemoglobin values usually are between 11.7 - 15.7 g/dL: For men, hemoglobin values usually are between 13.3 - 17.7 g/dL. Hemoglobin was calculated from frozen whole blood and should be repeated in a fresh blood sample.
Hemoglobin	7 g/dl - 11.6 g/dl if female; 7 g/dl - 13.2 g/dl if male		Abnormal		Your hemoglobin is low. You should check with your physician about this. Hemoglobin was calculated from frozen whole blood and should be repeated in a fresh blood sample.

Measurement	Threshold Values / Trigger conditions	Reported to participant as:			Script for Report
Hemoglobin	<7 g/dL			Alert	Your hemoglobin value is very low. You should check with your physician about this. Hemoglobin was calculated from frozen whole blood and should be repeated in a fresh blood sample.
Hemoglobin	>15.7 g/dl if female; >17.7 g/dl if male		Abnormal		Your hemoglobin is high. You should check with your physician about this. Hemoglobin was calculated from frozen whole blood and should be repeated in a fresh blood sample.
Glycosylated hemoglobin	HbA1c	Can use 'Normal' cover letter			Normal A1c values are less than 5.7% for someone who does not have diabetes. A result between 5.7 and 6.4% can indicate prediabetes (a high risk of developing diabetes). A result of 6.5% or higher may indicate diabetes. You should check with your physician about this. If you have previously been diagnosed with diabetes, please follow your physician's guidelines.
Serum potassium	Serum potassium (K) 2.6 – 5.9 mmol/L	Normal			Normal potassium levels in the blood are 3.3-5.1 mmol/L
Serum potassium	Serum potassium (K) <=2.5 mmol/L			Alert	Normal potassium levels in the blood are 3.3-5.1 mmol/L. A potassium level of 2.5 mmol/L or lower can be dangerous. Please check with your physician about this right away.
Serum potassium	Serum potassium(K) >=6.0 mmol/L			Alert	Normal potassium levels in the blood are 3.3-5.1 mmol/L. Having a blood potassium level higher than 6.0 mmol/L can be dangerous. You should check with your physician about this as soon as possible.
Serum magnesium	Serum magnesium (MG) (mg/dL)	Can use 'Normal' cover letter			Normal values of magnesium in the blood for adults are 1.6-2.6 mg/dL.
Serum albumin	Serum albumin (ALB) >= 3.5 (g/dL)	Normal			Normal levels of albumin in the blood are approximately 3.5 to 5.2 g/dL
Serum albumin	Serum albumin (ALB) < 3.5 (g/dL)		Abnormal		Your serum albumin result was low. This may indicate decreased liver or kidney function. Please discuss the serum albumin results with your physician.

Measurement	Threshold Values / Trigger conditions	Reported to participant as:			Script for Report
Kidney function	Fixed Text				ARIC estimated glomerular filtration from both creatinine and cystatin for more precise measurement of kidney function, especially in older adults (Inker et al., NEJM, 2012;367:20-9).
Serum creatinine	Creatinine (CR) <= 2 mg/dl	Normal			Normal levels of creatinine in the blood are approximately 0.5 to 1.2 mg/dL in men, and 0.4 to 1.1 mg/dL in women.
Serum creatinine	Creatinine (CR) > 2 mg/dl			Alert	Your serum creatinine result was high. This may indicate a decreased kidney function. Please discuss the creatinine and the estimated glomerular filtration rate (eGFR) results with your physician
eGFR (creatinine and cystatin)	eGFRcr-cys >=60 mlL/min/1.73 m^2	Normal			Your estimated glomerular filtration rate (eGFR) was calculated from the amount of creatinine and cystatin in your blood. Your eGFR is greater than 60 mL/min/1.73 m^2, which suggests that your kidneys are working well.
eGFR (creatinine and cystatin)	eGFRcr-cys 30- < 60 mL/min/1.73m^2		Abnormal		Your estimated glomerular filtration rate (eGFR) was calculated from the amount of creatinine and cystatin in your blood. An eGFR persistently less than 60 mL/min/1.73 m2 is an indicator of decreased kidney function and potential chronic kidney disease. You should discuss these results with your healthcare provider within a month.
eGFR (creatinine and cystatin)	eGFRcr-cys < 30 mL/min/1.73m^2			Alert	Your estimated glomerular filtration rate (eGFR) was calculated from the amount of creatinine and cystatin in your blood. An eGFR persistently less than 30 mL/min/1.73 m2 indicates severely decreased kidney function. You should discuss this result with your health care provider as soon as possible.
Urine albumin: creatinine ratio	ACR < 30 mg/g Cr	Normal			The level of albumin, the major protein in your urine, is in the normal range.

Measurement	Threshold Values / Trigger conditions	Reported to participant as:			Script for Report
Urine albumin: creatinine ratio	ACR >= 30 mg/g Cr		Abnormal		The amount of albumin, the major protein in your urine, is moderately elevated and may indicate chronic kidney disease. You should discuss this result with your healthcare provider.
Albumin: creatinine ratio (albumin)	Ratio >= 300 mg/g			Alert	The amount of albumin, the major protein in your urine, is elevated and may indicate chronic kidney disease. You should discuss this result with your healthcare provider as soon as possible.

21 Overview of General Quality Control Procedures

21.1 INTRODUCTION

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. Quality assurance is the essence of this 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 content of this Manual of Operations.

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 CC relies on study coordinators and certifiers 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 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. 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 may be taken by the same and different technicians to be 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 may be 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.

21.2 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.

Prior to Visit 7, multi-day central training covered all aspects of the study protocol, led by individuals with specific expertise in the given exam component. Attendance at these centralized training was strongly encouraged for all study personnel. At Visit 7, which followed 6 weeks after the close of Visit 6, the CC held a one-day refresher meeting for a limited number of study coordinators that enabled ARIC to move to 'train the trainer' model for Visit 7 procedures. With

current and upcoming visits following so closely to one another, central trainings will be replaced with on-site refreshers conducted by site personnel and/or virtual training webinars. For new visit components and ancillary studies, expert personnel will plan and conduct the training, which may include on-site training.

Staff must be certified in order to collect data and certification should be reported as described in the Certification Request Form available on the ARIC secure website [Cohort > Documents > *select current visit*]. Unless otherwise specified, the specific criteria and requirements for training in these areas are described in detail in the similarly named sections of this manual. 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 the component-specific sections of this manual. 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.

For study components certified by the Study Coordinators, the Study Coordinator will submit a Certification Request Form (located on the ARIC website [Cohort > Documents > CDART or *select current visit*]) 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. For new staff, the CC will assign a staff code number upon receipt of this form. Should existing 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. Some study components may require training and certification by a designated trainer outside the field site (see Table 2 in the Certification Request Form). For these components, trainers should notify the CC via arichelp@unc.edu of completed certifications. Additionally, the CC should be notified of any lapses in certification so that accurate certification and expiration dates are maintained for all study staff.

The CC will continually update records of all certifications at each study center, and staff code numbers will be compared against the neurocognitive 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 QCC, 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.

Unless stated otherwise, ARIC staff that have maintained certifications from the previous visit are not required to be recertified for procedures and techniques for the upcoming visit, except for staff who perform Biospecimen Collection and Processing (Note: biospecimen collection is not relevant for Visit 8 or 10, see Manual 7 for details). All staff who conduct new procedures will undergo training and certification for the new components.

Further, because the ACHIEVE ancillary study and the ARIC NCS Visits overlap in many aspects, there are instances in which the certification and equipment monitoring procedures can be the same (and done once) for the two studies.

a. CDART Certification Snapshot Report

Both ARIC and ACHIEVE study coordinators have access to the Certification Snapshot report in CDART. This report is found within the study called CSCC in the study menu. The report allows the study coordinator to review the certifications for a given staff member to ensure all certifications are tracked accurately. Any errors or omissions should be reported to the CC via arichelp@unc.edu with an updated Certification Request Form submitted as needed.

21.3 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 QCC is designated by the ARIC Steering Committee to coordinate and direct the quality control activities. This committee meets as needed 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 field center-specific completeness of data acquisition and other indicators of performance as proposed by the QCC or the Steering Committee, 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; identify a solution to each problem; implement corrective action; report corrective action to CC/QCC.
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.

21.4 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 may 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).

a. 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. QC reporting is found in the study management reports, study dashboards, and reporting to certifiers. The reports may contain the following information:

1) Repeated measures (if applicable)
2) Descriptive statistics
3) Timeliness and completeness of data entry

b. Replicate Data Analysis

When applicable, 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.

During analyses on QC replicate pairs, the data are screened for possible mismatches or "strange" observations. For instance, if a pair is an outlier for multiple assays this may suggest a labeling or processing error rather than assay variability.