Manual 2
Home and Field Center Procedures
ARIC-NCS Visit 6 Study Protocol

Version 1.0 – July 7, 2016

(Revised 3/9/17)

ARIC-NCS Visit 6 Study Protocol

Manual of Operations 2 - Home and Field Center Procedures

Table of Contents

(Pages are numbered within sections)

1. OVERVIEW 1-1

2. LIST OF ABBREVIATIONS 2-1

3. RECRUITMENT 3-1

3.1 Overview 3-1
3.2 Recruitment of proxies and informants 3-1
3.3 Linking the ARIC Follow-up Calls and the ARIC visit 6 examination 3-2
3.4 Recruitment of spousal pairs 3-3
3.5 Time Window for ARIC visit 6 3-3
3.6 Scheduling of Visit 6 examinations 3-3
3.7 Home/LTC Examinations 3-8
3.8 Recruitment and Examination Goals by Center 3-9
3.9 Monitoring of Recruitment Performance 3-9
3.10 Examination of ARIC Participants Who Relocate Near Another ARIC Center 3-10

4. HOME/LONG TERM CARE FACILITY EXAMINATIONS 4-1

4.1 Eligibility for a Home / LTCF Examination 4-1
4.2 Scheduling and Setting up a Home Examination 4-1
4.3 Conducting the Home Visit Examination 4-2
4.4 Processing, Transportation and Shipping of the Biospecimens 4-5
4.5 Abbreviated examinations at the ARIC field center 4-5
4.6 Training, Certification of Personnel 4-5
4.7 Quality Assurance 4-6

5. FIELD CENTER EXAMINATION – PROCEDURES AND INTERVIEWS 5-1

5.1 Overview 5-1
5.2 Abbreviated (Core) Exams and Mini Exams 5-3
5.3 Making an Appointment 5-3
5.4 Participant Safety Screening 5-4
5.5 Scheduling the Participant's Medications on the Day of the Examination 5-4
5.6 Appointment Reminders and Instructions for the Clinic Examinations 5-6
5.7 Split Field Center Examinations 5-6
5.8 Sequence of the Field Center Examinations 5-6
5.9 Participants Seen at a Different ARIC Field Center 5-7

6. RECEPTION 6-1

7. INFORMED CONSENT 7-1

7.1 Administration 7-1
7.2 Training and Certification 7-1
7.3 Data Collection 7-2
7.4 Ability to Comprehend the Informed Consent 7-2

7.5 ARIC/NCS Informed Consent Proxy and Informant Triggers 7-3
7.6 Defining the Need for Proxy Consent or an Informant 7-3
7.7 Recruitment of the Exam Proxy 7-4
7.8 Administration of the Informed Consent by Proxy 7-5
7.9 Consent Tracking Form 7-5
7.10 Procedures to Follow During the ARIC Exam if a Participant Restricts Consent 7-6
7.11 Procedures to Remove a Participant from the Study 7-7

8. BIOSPECIMEN COLLECTION – PLEASE SEE ARIC VISIT 6 MANUAL 7 8-1

8.1 Collection of the urine specimen 8-1
8.2 Blood Drawing and Processing 8-1
8.3 Staff Certification Requirements 8-2

9. ANTHROPOMETRY 9-1

9.1 Equipment and Supplies 9-1
9.2 Staff 9-1
9.3 Anthropometry Form 9-1
9.4 Examination Procedures 9-1
9.5 Quality Assurance/Quality Control 9-8

10. COGNITIVE FUNCTION 10-1

10.1 Overview 10-1
10.2 Administration – Overview 10-1
10.3 Mini-Mental State Examination (MMSE) 10-3
10.4 Delayed Word Recall Test (DWRT) 10-3
10.5 Digit Symbol Substitution test (DSST) 10-4
10.6 Incidental Learning 10-4
10.7 Word Fluency (FAS) 10-4
10.8 Animal Naming 10-5
10.9 Trail Making Test (TMT) A & B 10-5
10.10 Logical Memory I and II 10-6
10.11 Digit Span Backwards 10-6
10.12 Boston Naming Test (BNT) 10-6
10.13 Smell Test 10-7
10.14 Stage II – Cognitive Status 10-7
10.15 Refusals and Discontinued Tests 10-10
10.16 Training, Certification, and Quality Control 10-10

11. HEARING ASSESSMENTS 11-1

12. INTERVIEWS 12-1

12.1 Overview 12-1
12.2 Neurologic History 12-1
12.3 Epworth Sleepiness Scale 12-1
12.4 Clinical Dementia Rating Scale (CDR) 12-2
12. 5 Personal History 12-3
12.6 Medication Survey 12-4
12.7 Smoking and Alcohol Use Form 12-6
12.8 SF-12TM General Health 12-7
12.9 Center for Epidemiologic Studies Depression Scale (CESD) Short Form & Hopelessness 12-8
12.10. Diabetes Questionnaire (DQF) 12-10

12.11 Diabetes Treatment Satisfaction 12-10
12.12 Physical Ability Questionnaire 12-11
12.13 Physical Activity 12-12
12.13 Hearing Handicap Inventory 12-13
12.14 Self-reported Hearing and Noise Exposure Form 12-14

13. SITTING BLOOD PRESSURE 13-1

13.1 Introduction, Equipment and Supplies 13-1
13.2 The Sitting Blood Pressure (SBP) form 13-2
13.3 Blood Pressure Measurement Procedures 13-2
13.4 Procedure for the OMRON HEM-907XL 13-6
13.5 Reporting the Blood Pressure Values 13-12
13.6 Equipment Maintenance 13-13
13.7 Inspection and Validation of the OMRON Sphygmomanometer 13-13
13.8 Glossary and References 13-16

14. PHYSICAL FUNCTION, UNINTENTIONAL WEIGHT LOSS AND ENDURANCE 14-1

14.1 Overview 14-1
14. 2 Short Physical Performance Battery (SPPB) 14-2
14.3 Administration of the SPPB Single Chair Stand 14-5
14.4 Administration of the SPPB Repeated Chair Stands 14-6
14.5 Administration of the SPPB Standing Balance 14-7
14.6 Administration of the SPPB 4 Meter Usual Walk 14-9
14.7 Grip strength 14-10
14.8 Administration of the Unintentional Weight Loss Questions 14-13
14.9 Administration of the TMW 14-13
14.10 Safety Issues and Exclusions 14-14
14.11 Assessment of test eligibility and exclusion criteria. 14-15
14.12 Quality Control 14-20
14.13 Training and Certification for Grip Strength Assessment 14-20
14.14 Training and Certification for the TMW 14-20
14.15 Quality Assurance/Certification Checklist 14-21

15. PERIPHERAL NEUROPATHY ASSESSMENT – MONOFILAMENT TESTING 15-1

15.1 Overview 15-1
15.2 Background 15-1
15.3 Procedures 15-2
15.4 Explaining the Monofilament Testing 15-4
15.5 Sites to be Tested 15-4
15.6 Standard Procedures 15-5
15.7 Definition of Responses 15-6
15.8 Determination of Peripheral Neuropathy 15-6
15.9 Data Collection Elements 15-6
15.10 Order of Test Sites and Assigned Intervals to Apply the Monofilament 15-7
15.11 Reporting the Test Results to Participants 15-8
15.12 QUALITY ASSURANCE 15-9

16. ADDITIONAL ANCILLARY STUDIES 16-1

16.1 ZIOPATCH 16-1
16.2 ABI AND PULSEWAVE VELOCITY 16-1

17. DATA INVENTORY 17-1
18. EXIT INTERVIEW 18-1
19. PARTICIPANT SAFETY 19-1
19.1 Measures to Protect the Participant 19-1
19.2 Procedures for Handling Emergencies 19-2
19.3 Major emergencies 19-2
19.4 Minor emergencies 19-3
19.5 Emergency Equipment 19-4
19.6 Procedures to Define and Report Adverse Events and Unanticipated Problems 19-5
19.7 Adverse Events and Unanticipated Problems - Definition and Reporting in ARIC 19-5
19.8 Definition and Classification of AEs in ARIC 19-5
19.9 Definition and Classification of UPs in ARIC 19-6
19.10 Reporting of Adverse Events and Information Flow 19-7
19.11 Exclusions from Study Procedures 19-9
19.12 Stopping Rules for Interviews and Procedures 19-9
20. REPORT OF STUDY RESULTS, MEDICAL REFERRALS AND NOTIFICATIONS 20-1
20.1 Procedures for Medical Referrals and Notification of Results 20-1
20.2 Medically Relevant Information 20-1
20.3 Quality Assurance 20-3
20.4 Actionable Study Results 20-3

Appendices

Appendices are identified by section number in Manual 2, and are found in the secure section of the ARIC study Website (https://www2.cscc.unc.edu/aric/) under Cohort -> V6/NCS -> V6/NCS Manuals

Appendix 1.

- Appendix 1.A Prototype Recruitment Letter
- Appendix 1.B Visit 6 Scheduling Script
- Appendix 1.C Prototype Appointment Letter
- Appendix 1.D Aric Medication Instructions (included in the clinic packet)
- Appendix 1.E Clinic Appointment Reminder
- Appendix 1.F Home Appointment Reminder
- Appendix 1.G Proxy/Informant Recruitment
- Appendix 1.H Scheduling Of Aric Participants In Alternate Field Centers

Appendix 2 Field Center Examination Checklist

Appendix 3 Prototype Cover Letters and Instructions for Reporting of Study Results

1. OVERVIEW

This manual of operations on Home and Field Center Procedures is one of a series of manuals of operation for the Atherosclerosis Risk in Communities (ARIC) Study. The fifth re-examination of the ARIC cohort (ARIC Visit 6) is conducted under the auspices of the ARIC Neurocognitive Study (ARIC-NCS) and is referred to here as ARIC Visit 6.

The breadth of characterization of the ARIC cohort requires separate manuals of operation which have been organized into a set of study protocol manuals. Manual 1 provides an overview of the background, aims, organization, and general objectives of the cohort re-examination. Manual 2 refers to the recruitment of the ARIC cohort to its 5th re-examination and details the interviews and clinical measurements conducted as part of the ARIC Visit 6 field center and home examinations, cross-referencing the procedures set out in other ARIC Visit 6 protocol manuals. The procedures and interviews are presented below approximately in the order in which they occur, and in alphabetical order within blocks of interviews. Tables 4.1 and 5.1 list the main components of the field center and home examinations, with reference to their respective study forms.

High quality of data and a strict standardization of the interviews and examination procedures across all field sites and throughout the duration of the study are essential for the success of the ARIC-NCS. This requires that all ARIC-NCS field center personnel be fully familiar with this manual of procedures, be fully trained and certified in the procedures described in ARIC Manual 12 (Quality Assurance and Control), and remain standardized throughout the data collection phase. Mastery of the procedures described in this manual is required so that patterns in the ARIC-NCS data can reflect differences between study participants and their characteristics as opposed to differences between study technicians or study center.

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, an overview of training requirements and certification criteria, routine quality assurance measures, and data collection procedures.

2. LIST OF ABBREVIATIONS

ARIC	Atherosclerosis Risk in Communities Study
ALT	Serum alanine aminotransferase
AST	Serum aspartate aminotransferase
NCS	Neurocognitive Study
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute on Aging
NIH	National Institutes of Health
CDART	Carolina Data Acquisition and Reporting Tool
CSCC	Collaborative Studies Coordinating Center
eGFRcr-cys	Estimated glomerular filtration rate calculated from serum creatinine and cystatin
EPICARE	Epidemiological Cardiology Research Center
DBP	Diastolic Blood Pressure
GGT	Serum gamma-glutamyltransferase
HbA1c	Glycosylated hemoglobin
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
LTCF	Long term care facility
MOP	Manual of operations
QxQ	Question by question
SBP	Systolic Blood Pressure

3. RECRUITMENT

3.1 OVERVIEW

The purpose of this section is to provide information on the recruitment procedures for ARIC visit 6. These procedures aim to obtain the highest participation rate among eligible cohort members.

Recruitment and scheduling of participants will proceed as follows. First, it will be necessary to determine whether the participant will attend the clinic or will require a home or long-term care facility (LTC) visit. At the same time, it will be necessary to determine whether the participant needs to be accompanied by a proxy at the time of the visit (either in the clinic or at home/LCTF).

3.2 RECRUITMENT OF PROXIES AND INFORMANTS

Similarly to the ARIC visit 5 exam, ARIC visit 6 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.

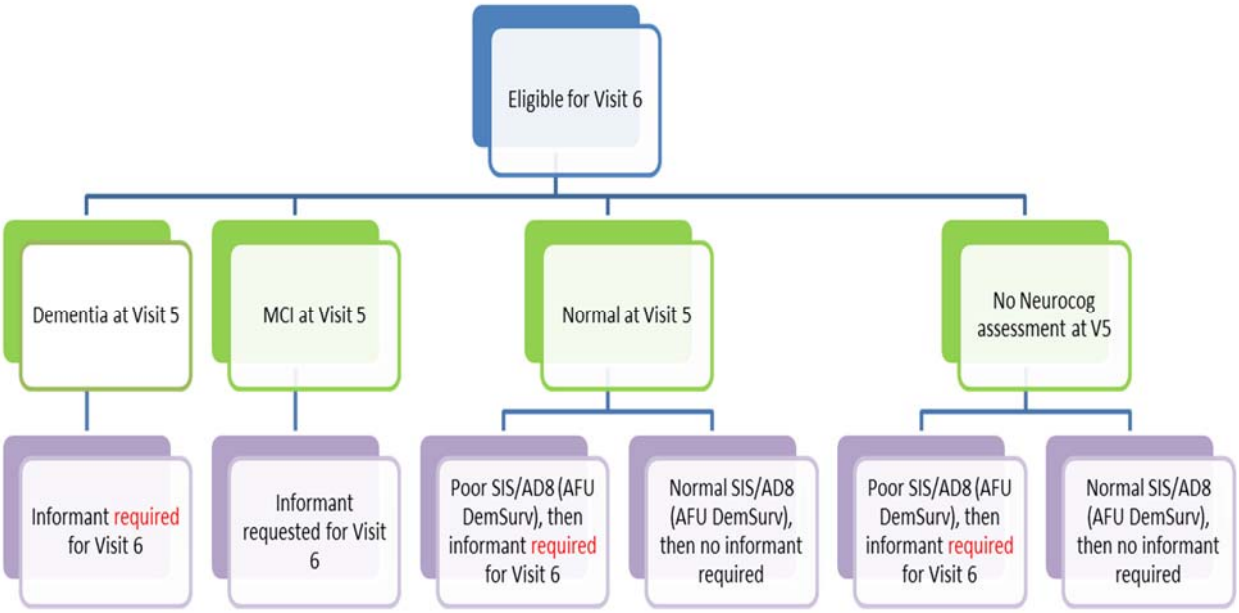
This section provides study-wide definitions for these roles when exercised on behalf of the ARIC participants, general guidance on the criteria by which the need to engage a proxy or informant is determined, and describes their role in recruitment. An exam proxy is a person who can provide informed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

As part of the ARIC visit 6 exam all participants will update the information on their proxy respondent (or will identify one if not already done) for purposes of cohort follow-up. This is a person designated by the participant to provide medical information about the participant to ARIC personnel and/or to 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 ARIC's follow-up.

An informant is a person sufficiently familiar with the participant's daily activities to be able to provide adequate information on the behaviors and 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.

The algorithm below provides information on the need of having a proxy/informant accompany the participant during ARIC visit 6 (whether it is a clinic or home/LTC visit). In general, participants who received an ARIC diagnosis of dementia or mild cognitive impairment (MCI) at the time of ARIC visit

5/NCS will require a proxy/informant for visit 6. Similarly, those who did poorly in the Six Item Screener (SIS) / AD8 test as part of the dementia surveillance in any AFU after visit 5/NCS will be asked to bring a proxy/informant.



Finally, if at the time of the ARIC visit 6 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/LTC or clinic). This decision can be aided by using the Six Item Screener at the time of recruitment.

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 a 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 (based on the previously stated criteria) 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.

3.3 LINKING THE ARIC FOLLOW-UP CALLS AND THE ARIC VISIT 6 EXAMINATION

In earlier exam visits recruitment of ARIC participants occurred at the time of the annual ARIC follow-up phone call. ARIC visit 5/NCS followed a different approach to fit within the two-year examination time, to accommodate high risk cohort members, and to allow for home and LTC visits.

Systematic approaches to recruitment were avoided however to reduce possible drift or bias in the data collected.

The timeline for ARIC visit 6 requires recruiting and scheduling all participants during an 18-month period. 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 their 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 has created a recruitment report in CDART that includes 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 includes information on several variables that facilitate the identification of high-risk individuals (i.e. those more likely to refuse), such as frailty, dementia diagnosis, cognitive status at the last cognitive assessment in follow-up calls (using SIS or AD8 forms), and others. The report also includes information on variables required to determine eligibility to the falls substudy (visit 5 MMSE score, completion of visit 5 4-meter walk).

Using the recruitment report, the field centers have flexibility in scheduling their study participants, with the goal of achieving a high response rate and accommodating their study participant's needs. Scheduling of the visits can occur during the ARIC follow-up call, or in a separate call if circumstances require this. In contrast to ARIC visit 5/NCS, it will not be required to schedule separate Stage 2/3 visits.

3.4 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 6 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.

3.5 TIME WINDOW FOR ARIC VISIT 6

The field work is scheduled to extend for 18 months. Scheduling of participants begins approximately 1 month prior the start-up of field work.

3.6 SCHEDULING OF VISIT 6 EXAMINATIONS

a. Overview

The steps in the scheduling of procedures for Visit 6 are similar to those for scheduling and conducting the ARIC Follow-up Interview, but also include determining whether the participant will require a home/LTC 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 ARIC Visit 6 will be set. A brief description of Visit 6 is provided in the letter, as well as a request to have a calendar available to facilitate scheduling Visit 6. An ARIC newsletter explaining the main goals of the exam can be included in this mailing. A letter template is provided in Appendix 1.A.

The cohort member is contacted by telephone and the ARIC follow-up call is conducted in the usual manner. 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. The location of the ARIC field center is mentioned and, if possible, an appointment for Visit 6 at the exam site is scheduled.

The participant is asked about any special arrangements for the examination visit, such as medical treatments, transportation, 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 is 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 by ARIC staff to conduct an interviews and a brief physical examination is suggested. Cohort members who are unable to leave their home or are residents of a LTC 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 with an online link to an informed consent video that provides details about the different 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 and the questions prior to the appointment data are encouraged. The procedures are modified for examinations to be performed at the home or in LTC facilities.

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 fasting requirements, collection of all medications and supplements for review at the field center, adequate clothing 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 Coordinating Center generates from the ARIC database a list of cohort members to be contacted for Visit 6 and their contact month. The list is similar to that provided for AFU calls, and is generated well in advance of the contact window to allow field centers to trace and schedule hard to find cohort members, snowbirds, and out-of-state residents. See above.

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 distributed to the field centers by the Coordinating Center. 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 – visit 6 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 Coordinating Center 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 6 exam are made as part of the ARIC Follow-up call, if possible. Otherwise, the ARIC follow-up and recruitment calls are performed separately. Each field center keeps track of both AFU completion and Visit 6 recruitment status for all selectees (using the RTS form), with overview provided by the Coordinating Center in periodic reports to the Steering Committee.

d. Making the exam appointment

After completing the AFU interview for all cohort members in a household, the interviewer describes the exam, including the new components, and schedules the participant's Visit 6 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 inquires about several items to assist in scheduling the appointments:

- Preferred time and date of examination
- Establish how participants prefer to get there
- Determine 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 getting to or moving around the clinic
- If home visit is required, information on home safety issues and availability of adequate space, and if at a LTC 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. When possible, cohort members are scheduled for appointments at their convenience, including scheduling all eligible members of a single household for examinations on the same day whenever possible.

In the case that 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 LTC 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 LTC, a reminder call will also be made to the facility, though each participant in a LTC will be approached in a case by case basis (see below for information on home and LTC 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 LTC 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 on how to complete the 8-hour fast. Note: for home/LTC visits, fasting is preferred but not absolutely required
    - Instructions on proper hydration while maintaining the fast.
    - 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
- 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/LTC (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)

- Document with link to online informed consent video

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.

3.7 HOME/LTC EXAMINATIONS

Similarly to Visit 5, Visit 6 will offer the possibility of scheduling home or LTC visits for those cohort members unable or unwilling to participate in the clinic exam. Overall, each field center should aim to have as many participants 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, we expect that approximately 15% of the exams will be home/LTC visits and the field centers should plan accordingly.

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 taking care of another person
- Preference: if the only way a cohort member is willing to participate in the new exam is with a home visit, the field centers should try to 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 appendices 2 and 4).

a. Scheduling of Examinations at LTC Facilities

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 LTC. During this call,

the recruiter will obtain contact information for the LTC and how best to approach the cohort member.

2. Once information on the facility is obtained, an explanatory letter will be sent to the LTC 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 LTC. 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 LTC, recruitment staff will phone the LTC 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 LTC 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 LTC caregivers in this decision.

3.8 RECRUITMENT AND EXAMINATION GOALS BY CENTER

It is estimated that approximately 4214 ARIC participants will be examined in Visit 6, with 675 being home or LTC exams. These numbers correspond to approximately 169 home visits and 885 clinic exams per field center (with some variability across centers). In order to finish in 18 months, field centers should aim to complete approximately 13-16 clinic exams and 2-3 home/LTCF visits per week (possibly more in those field centers with more living participants).

Projected visit 6 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/LTC 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.

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.

3.9 MONITORING OF RECRUITMENT PERFORMANCE

Interviewers scheduling examinations report appointment information to their field center on a daily schedule. Sufficient appointments are scheduled each day from Monday through Friday to meet the requirements of approximately 13-16 clinic exams and 2-3 home/LTC visits per week.

Each field center maintains the following scheduling documentation:

- A listing of cohort members by ID or name, with telephone number and other contact information (Contact Information Update (CIU) Form)
- Tracking forms for each cohort member (Recruitment Tracking and Scheduling (RTS) Form). One form per cohort member to track and document the status of each attempt to recruit them to the Visit 6 exam.
- 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.

3.10 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 Coordinating Center 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 Coordinating Center 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 copies 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 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.

3.11 Training and Certification of Follow-up and Recruitment Personnel

Interviewers are trained and certified in general interviewing techniques and the administration of the AFU form. This requires familiarity with the contents and procedures for administering the AFU form, assigning contact and appointment status codes on the AFU Record of Calls, scheduling a field center appointment, and verifying contact information on the Contact Information Update form. Staff is certified centrally. Recertification is required annually with the recommendation of periodic refresher courses and retraining if quality assurance analyses indicate poor performance or inconsistent results. The training and recertification requirements apply to any staff in charge of

recruitment, even if they do not conduct AFU calls (in some situations, AFU and recruitment might be independently conducted).

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 (LTC), 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-NCS field center. The examination at the participant's home or LTCF is an abbreviated assessment which includes the Visit 6 exam component shown in Table 4.1. 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 items to be acquired. The expected duration of the home visit is approximately 180 minutes (195 minutes if the study participant has diabetes).

4.1 ELIGIBILITY FOR A HOME / LTCF EXAMINATION

The ARIC Coordinating Center 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 LCTF 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 assembles the home examination materials on the day before the home visit: the participant ID labels are printed and the biospecimen collection tubes are labeled per the Biospecimen Collection Protocol and placed in the home examination kit. The cognitive testing materials include the bound testing booklet, pencils, stopwatch, and cognitive stimulus materials. The equipment required includes: professional scale (McKesson), home biospecimen collection kit and biospecimen collection supplies, small container with ice (for EDTA tubes), the OMRON blood pressure monitor, a laptop computer equipped with the secure ARIC data entry and management system, and a barcode reader. 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 DVD (and the informed consent forms at the field center's discretion) are mailed to the study participant – and to the proxy, an informant or relative as applicable – in advance of the home visit. One week is allowed for these materials to be reviewed prior to the home visit. 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, at which 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 LTC facility are conducted using the ARIC-NCS 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/quality control protocol applies.

Table 4.1 Visit 6 ARIC-NCS Home and "Core" Field Center Examination Components, Listed in their Recommended Sequence

ARIC-NCS Home/LTC Stage I Examination Components§	Forms	Ppt. or Informant	Ppt. Time (min.)
Informed Consent	ICT	Ppt (Inf)	20
Update of contact/proxy/tracking information	CIU	Ppt	6
Weight, seated blood pressure	ANT/SBP	Ppt	10
Blood draw, urine specimen	BIO	Ppt	15
Snack	--	Ppt	15
Cognitive Testing Block A (cognitive functional status): MMSE, Delayed Word Recall, Digit Symbol Substitution, Incidental Learning, FAS, Animal Naming, Trails A&B[1]	MME, CNF	Ppt (Inf)	30
Neurologic history and CDR Participant	NHX, CDP	Ppt	10
Auditory testing	AUD, HHI	Ppt	25
Peripheral neuropathy testing	PNF	Ppt	10
Personal history, medications, smoking and alcohol use, SF-12, diabetes questionnaire, diabetes treatment satisfaction	PHX, MSR, ALC, SFE, DQF, DTS	Ppt (Inf)	29 (+10 if diabetic)
ZioPatch application and instructions		Ppt	5
Exit interview		Ppt (Inf)	10
Cognitive status: informant interview[2]	CDI, NPI		n.a.

Estimated times: Participant: 175 min (185 min if participant has diabetes)

1: CDI to be collected primarily by phone after the exam, based on cognitive performance, but may occur at the field center or home, depending on informant availability. The CDI is not collected on participants diagnosed with dementia at V5.

§: Shaded area: fasting portion of the examination, without caffeinated beverages

If the home/ LTC visit is limited by time restrictions, the Neurocognitive Test Battery Block A is given priority, and should occur immediately after the MMSE (which is the minimum that should be included in the home/LTC evaluation).

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 blood test results 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 LTC facility are specified in MOP 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 are 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 better as well as standardized environment for the examination. The contents of a 'home examination' conducted at an ARIC field center do not differ from those conducted at a home, but the field center exam protocol procedures 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 EXAMINATION – PROCEDURES AND INTERVIEWS

5.1 OVERVIEW

The ARIC-NCS examination is a fully standardized sequence of interviews and procedures conducted according to a common protocol. The components of the Visit 6 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. Study participants are asked to fast for at least 8 hours and to abstain caffeinated beverages and from smoking on the morning of their ARIC examination. Following the participant's informed consent a first set of procedures and examinations is conducted in the fasting state since food intake affects the quality of the data. This group of procedures is shown in the shaded portion of Table 5.1, prior to the participant's breakfast or snack. With the exception of the informed consent, the procedures performed in the fasting state can be administered in any sequence while the participant is fasting. Consumption of caffeinated beverages should also be avoided during this time, until the participant is scheduled to have a snack.

Following the snack, the neurocognitive battery, identified in the table as Cognitive Testing Block A is administered first, followed by a brief break and Cognitive Testing Block B. The remaining procedures and interviews preceding the exit interview can be administered in the order best suited to an efficient exam flow at each field center.

Table 5.1 ARIC-NCS Visit 6 Field Center Examination Components, in order of Administration			
Examination Components - Field Center	Forms	Field Ctr.	Ppt.Time (min)
Informed Consent (video and informed consent document)	ICT	*	25
Updates to Contact Information	CIU	*	5
Participant safety screen / Itinerary	PSA	*	3
Change of Clothes, Collection of Urine Specimen	BIO	*	10
Anthropometry, Seated Blood Pressure	ANT, SBP	*	12
Blood Draw, Biospecimen Processing	BIO	*	18
Snack	--	*	15
Cognitive Testing Block A (cognitive functional status): MMSE, Delayed Word Recall, Digit Symbol Substitution, Incidental Learning, FAS, Animal Naming, Trails A&B;[2]	MME, CNF	*	30
Break		*	5
Cognitive Testing Block B: Logical Memory I, Digit Span Backwards, Boston Naming, Smell test, Logical Memory II.	CNF	*	25
Audiometry testing	AUD, HHI	*	25
Interviews Block A: Neurologic history, Epworth Sleepiness Scale, CDR Participant	NHX, CDP, ESS	*	10
Lunch		*	30
Interviews Block B: income, medications, smoking and alcohol use, SF-12 health survey, general preventive care practices, diabetes questionnaire, depression	PHX, MSR, ALC, SFE, DQF, DTS, CES	*	29 (+ 10 if diabetic)
Peripheral neuropathy testing	PNF	*	8
Physical function testing, 2 minute walk	PFX, TMW	*	12
Interview Block C: physical abilities, unintentional weight loss, hearing handicap inventory, self-reported hearing and noise exposure, activity level	PAQ, GNB, HHI, HNE, PAC	*	15
ZioPatch application and instructions		*	5
Change of Clothes	--	*	10
Falls sub-study (n=400) Falls Hx, falls efficacy scale, falls risk self-assessment, instructions (falls calendar, accelerometer, physical activity tracking)	FRM, FES, FRC, FCL, FCF	*	24
Exit interview (end-of-visit report; review of alerts)	--	*	10
Cognitive status: informant interview[3]	CDI, NPI	Phone	n.a.
Approximate participant time excluding Falls sub-study: 5 hours			

§: Shaded area: fasting portion of the examination, without caffeinated beverages

1: See also Table 7.1 for interviews administered for participation under consent by proxy.

2: Participants diagnosed with dementia at V5 receive an only cognitive testing Block A.

3: CDI will primarily be collected by phone after the exam based on cognitive testing performance. In some cases, the CDI can be conducted in clinic/home, depending on proxy availability. The CDI is not collected on participants who were diagnosed with dementia at V5.

5.2 ABBREVIATED (CORE) EXAMS AND MINI EXAMS

Cohort members who are frail or find the ARIC-NCS examination too long or demanding may choose an abbreviated version, approximately 3 hours long. Although such an option is negotiated with the study participant the elements of the abbreviated examination are established by protocol, as set out in Table 4.1.

Exceptionally, participants who are infirm or unable to schedule a more extensive examination can be offered a Mini Exam – at home or the ARIC field center – that includes the informed consent (self/proxy), participant safety (PSA), weight and seated blood pressure (ANT, SBP), blood draw and collection of urine specimen (BIO), medication inventory (MSR), and an abbreviated neurocognitive assessment (the MMSE and the DWRT, DSST, FAS sections of the NCS). This is followed by an exit interview. A fasting status is preferred but not required, and the examinee may wear street clothes.

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. Interviewers make the number of call attempts specified for each ARIC field center, tracking them on an exam scheduling worksheet. 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.

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 fasting times or 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 (next section).

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 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 during the visit. 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.

-Individuals who have diabetes and take oral hypoglycemic medications can withhold them until the last blood draw and their snack. Participants who take insulin should be asked to withhold the morning dose until the blood draw and snack. Participants who use insulin should be advised to check their capillary glucose level two hours after the snack.

-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 accordingly; if this is not practicable the participant is asked to consult with their physician.

The study participant is reminded that the blood tests and other examination procedures require fasting for at least 8 hours prior to drawing blood and that a snack is provided about two hours after the start of the field center examination. Fasting means no consumption of food or drinks (including alcohol), with the exception of water. Participants will be asked to not consume food or drinks after midnight prior to the clinic visit and to refrain from smoking for the same length of time, or for 8 hours prior to the scheduled time of arrival at the field center. The participant is asked whether there are medical reasons for him/her not to be fasting for this length of time and alternate arrangements are made if necessary after consultation with the a supervisor. Study participants are then told what the options for the snack are at the field center and asked whether the participant has any dietary needs that are not met by these choices.

Key scheduling tasks are to 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

Examinations may be scheduled as split exams if the study participant is unable to take part in a full examination, or 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.

If an exam visit is discontinued after biospecimen was collected, this original venipuncture and specimen processing information is recorded in CDART and not repeated upon return of the participant. However, 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. Staff should note on the results report the updated Blood Pressure from the repeat visit. The ultimate intent is that the lab values and the blood pressure measurements are from the same time point.

5.8 SEQUENCE OF THE FIELD CENTER EXAMINATIONS

The sequence of examination procedures (participant flow) includes fixed and flexible components. Briefly, informed consent must be obtained prior to any data collection, followed by the collection of measurements that must be obtained in the fasting state. Following the snack the cognitive assessment is administered to minimize the influence of participant fatigue.

Following this point, each participant's itinerary is structured with exchangeable blocks of procedures and interviews that optimize participant and staff time. Field centers develop participant flow schedules that best fit their staffing pattern and facilities. Such participant itineraries reflect the number of examinees scheduled for the day, and are 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 on a board for convenient consultation by staff during the examination, also at the discretion of the field center.

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, that the on-site report of study results is printed for review with the participant, and that instructions are provided for the wearable devices such as the Ziopatch and the activity monitor, 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 Coordinating Center at least two weeks ahead of the scheduled visit. The Coordinating Center will grant temporary privileges to the visiting field center to access the participant's data in CDART [NOTE: Medication (MSR) data to be entered in CDART1 is the responsibility of the original field center]. 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 (with the exception of MSR) 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 Coordinating Center on a case by case basis.

When the clinic visit and its data entry have been completed, the original study site should contact the Coordinating Center 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 <u>not</u> duplicate what has been entered in CDART is also to be shipped to the participant's original center. This includes the MSR, as it is to be entered by the original site into CDART1.

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, fasting status is determined and the medication bag is logged and labeled.

Prior to the participant's visit information on mobility and special needs recorded on the Participant Safety Screening form (PSA) 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. At the time of the participant's arrival at the reception station, staff displays the Contact Information Update form in CDART and confirms the identifying information, address, and contact information with the study participant. The Participant Safety Screening 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 Participant Safety Screening form are confirmed with the participant; if not completed previously the Participant Safety Screening 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 view the informed consent video and to read and review the informed consent in consultation with ARIC personnel, as described in the next section. If the study participant has not viewed the informed consent DVD, s/he is given a copy of the informed consent form and asked to watch the DVD. No data collection can take place before informed consent has been obtained.

Once consenting procedures are complete participants are shown where to change into clothing worn during the ARIC examination. A gown, robe, smock or loose-fitting clothing can be used at the field center's discretion. Participants are reminded to remove all jewelry, to place clothing and valuables in a secured locker, and to keep eye glasses with them. 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 Section 8 of this manual and are reviewed with the participant.

Staff is 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 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 and 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. 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. An informed consent video has been prepared to support full comprehension of the informed consent (https://youtu.be/dlFq519-1QA, and http://www2.cscc.unc.edu/aric/aric_ncs_videos). At field centers' discretion, the informed consent can be mailed to the participant in the course of recruitment/exam scheduling, or played at the reception station to explain the purpose of the ARIC exam, its components, and the rights the cohort member as a study participant. Questions are encouraged, and time is allowed for the person to read and sign the informed consent document. 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 Informed Consent Tracking 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.

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. The participant’s score on the 6-item screener will guide ARIC staff in deciding whether to recruit a

Consent Proxy, and whether to alert an ARIC field center clinician to assess participant safety needs.

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 Informed Consent Tracking (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 6, his/her informed consent of reference is the latest informed consent provided to ARIC from ARIC exam visits 1-5, 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. ARIC cohort members who take part in Visit 6 under a consent by proxy are offered all study procedures that are not preempted by a safety exclusion, and a subset of the interviews as shown in Table 7.1. 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.

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. These include (any of):

- Staff assessment, at the time of annual follow-up interview, the examination scheduling call, or at the time of in-person informed consent. Because no mental status screen will identify all cases of cognitive impairment, the need for a proxy or informant will be informed by the judgment of the ARIC staff, with guidance from the study clinician (MD or RN).
- Impaired recall or some disorientation to time (a score <2 on the six-item cognitive screener), or disorientation to time (score = 0 on orientation items from six-item cognitive screener).

Note: A self-reported diagnosis of dementia/Alzheimer's Disease is not in itself a reason for requiring an alternate respondent.)

7.7 RECRUITMENT OF THE EXAM PROXY

Table 7.1 Visit 6 ARIC-NCS Home and "Core" Field Center Examination Components, Administered Under Consent by Proxy

ARIC-NCS Home/LTC Examination Components	Forms	Admin. to Participant	Amin. to Proxy
Informed Consent	ICT	Assent	Consent
Update of contact/proxy/tracking information	CIU		X
Weight, Seated blood pressure	ANT/SBP	X	
Blood draw, urine specimen	BIO	X	
Snack	--	X	X
Cognitive testing	MME, CNF, CPD	X	
Cognitive status: informant interview	CDI		X
Neurologic history	NHX		X
Auditory testing	AUD, HHI	X	
Monofilament testing		X	
Medications, smoking and alcohol use	MSR, ALC,		X
Exit interview		X	

If recruitment of a proxy is necessary at the time of recruitment for Visit 6 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]?"

If YES:

"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 Contact Information Update 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.

7.8 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. The disposition of data collected during the exam visit on a participant subsequently deemed to require a proxy/informed consent by proxy should be guided by consultation with the local IRB, and the ARIC coordinating center informed accordingly.

7.9 CONSENT TRACKING FORM

The Informed Consent Tracking (ICT) form is an internal form to monitor the level of consent given by study participants to participate in the ARIC and records 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 includes 9 items asking the participants whether they agree/disagree. The participant's instructions for each of the 9 items are recorded on the ICT. This form must be completed in the DMS within 3 days of the examination, since this form must be in the database for the ARIC coordinating center and central laboratories to perform the assays and specimen storage procedures according to the participant's instructions as recorded on the informed consent form.

The ICT includes an additional question (items 10 and 12.a on the ICT), to record whether the participant restricted access to his/her medical records. This is not an item found in the tiered

informed consent section that includes the 9 items listed above. Instead, item 10 of the ICT is based on the information included in the body of the informed consent form under the heading 'How will my medical records help ARIC?' (pagination may differ across centers).

ARIC participants have granted ARIC personnel access to their medical records since the inception of ARIC, as stated again in this consent form. If the participant does not 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. Item 10 of the ICT is answered *Agree* if this section of the informed consent was not amended in the process of obtaining informed consent. 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'.

Consent to Release Protected Health Information. After informed consent has been obtained the ARIC staff who administers the consent provides the participant with the pre-filled, but undated, consent to release Protected Health Information. If the participant agrees to sign such a release form for eventual use by the ARIC staff, this is entered in item 10a of the ICT form.

7.10 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 Coordinating Center 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 has restricted consent for specific questionnaires or measurements, these individual interviews and procedures are not collected at the time of the examination, and the corresponding data collection form(s) are recorded in the DMS as permanently missing. A different procedure is followed for the collection of the biospecimens and their processing. 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 the DMS). 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 MOP 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.

7.11 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 coordinating center 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;
- Threatening / antisocial behavior by the participant towards the staff or other study participants.

Administrative exclusion of an eligible participant recruited and/or examined by ARIC must be initiated or approved by the field center PI, and communicated to the coordinating center for adjustments to the field center's list of eligible enrollees, purging of the Exam 6 biospecimen repositories, adjustments to the collaborative database and analysis files, and to enable recognition of the former study participant by various study management tools.

8. BIOSPECIMEN COLLECTION – Please see ARIC Visit 6 Manual 7

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, preferably at the beginning of the clinical exam as the participant changes into scrub suits. After participants complete the Reception work station activities and are taken to change clothes, they are informed about the urine collection. 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.

Scripted instructions are provided in Manual 7. Bathrooms are equipped with a wall clock and pencils for participants to use in recording the time of voiding on the label. The staff member verifies the participant has written the "time voided" on the label, and assesses the adequacy of the sample for processing. At least 6 mL of urine is required for processing. If insufficient, the participant is requested to void again in a clean container prior to leaving the field center. A note is made on the participant's Itinerary sheet that a second urine sample is needed by the staff person who observes the placement of the participant's urine specimen in the refrigerator. The instructions for providing the urine sample are repeated to the participant at that time.

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. This can be done either by the participant or a staff member, as determined by local option. 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 not 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 are not be accurate even if the laboratory assays are precise. 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, fully compliant with the protocol for drawing and processing the specimens in the field, and also willing to take pride and responsibility in their work. The ARIC study collects approximately 80 ml of blood from each participant.

8.3 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 quarterly quality assurance and quality control analyses conducted by the coordinating center for the Quality Control Committee.

9. ANTHROPOMETRY

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 is not measured at ARIC's Visit 6.

9.1 EQUIPMENT AND SUPPLIES

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

- Tanita Body Composition Analyzer, TBF-300A
- (A wall mounted stadiometer is part of the ARIC workstation but not used in Visit 6)
- Gulick II 150 and 250 cm anthropometric tapes
- 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 the DMS 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 the DMS.

9.3 ANTHROPOMETRY FORM

The ANT form records anthropometry measurements in three sections: ability to stand (A), height (not measured in Visit 6), weight, bio-impedance output values from the Tanita scale (B) , and waist circumference (C). As the technician progress through the examination procedures, they record (or directly enter) results into the ANT form.

9.4 EXAMINATION PROCEDURES

For all measurements, participants should wear scrub suits or 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 Visit 6 (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)

b. Weight and Body Composition

Before taking any measurement on the digital scale, ask participants 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.

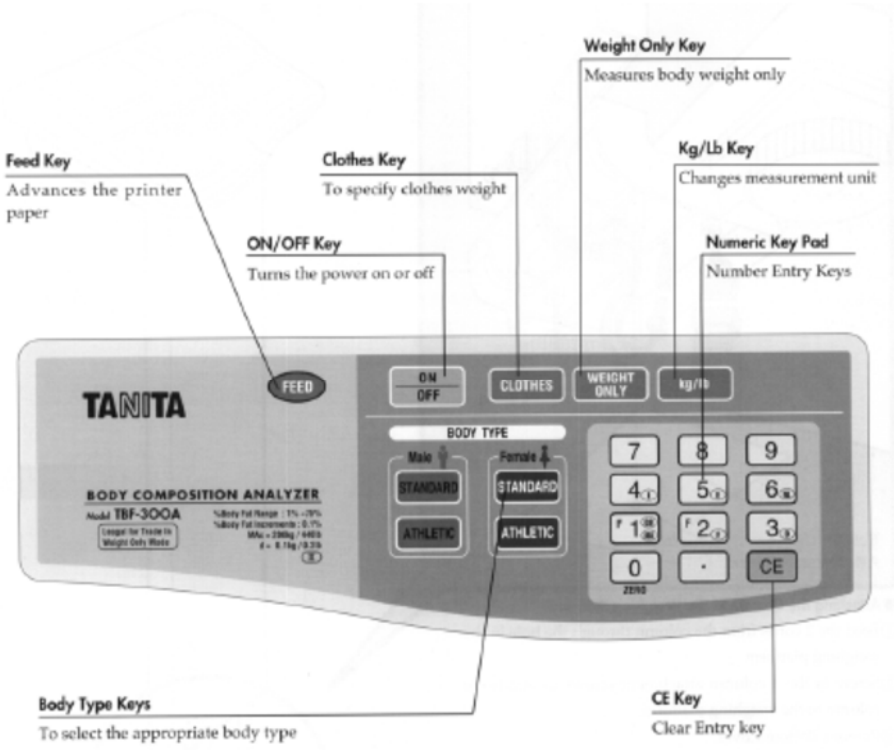


Figure 9.1 Control Panel of Tanita Body Composition Analyzer, TBF-300A

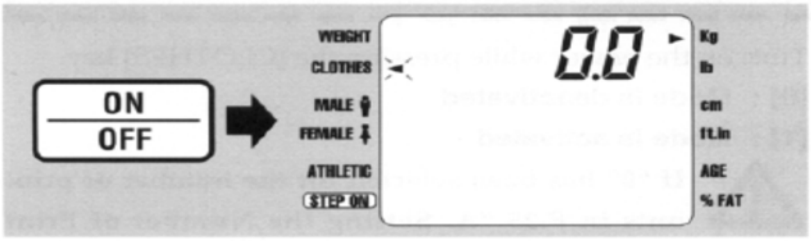
c. Initial set up

Place the scale platform on a flat and level surface, not on 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

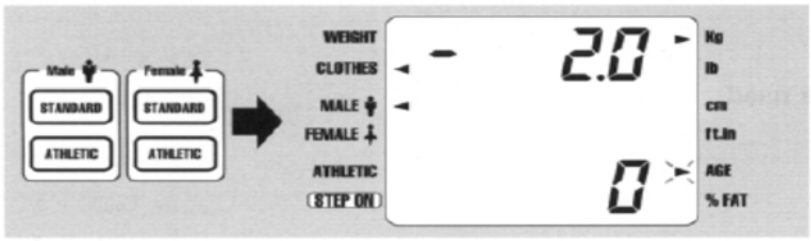
Press and hold the 0 key, and press the ON/OFF key once. Release the 0 key after “Prt-1” is displayed on the screen. Select 0 (no print out). When no print out is selected (there is no need to select the printing language). The panel will switch to the measurement screen.

e. Operating instructions

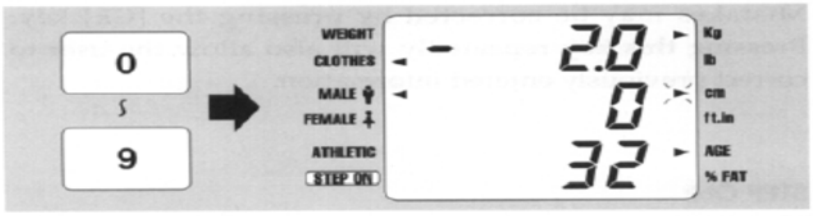


Press ON/OFF key to turn the machine on. Wait until 0.0 and an arrow appear on the screen. Check that the arrow points to “Kg”. If arrow point to “lb”, press the Kg/Lb key on the control panel and the arrow will shift to “Kg”

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

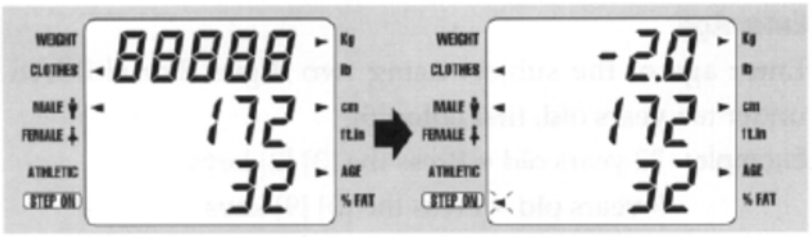


Select Gender and Body type: Standard Female or Standard Male

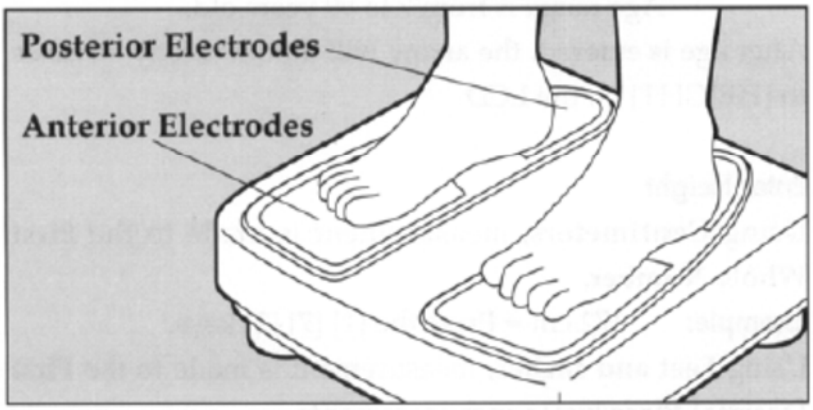


Enter age of participant using the numeric pad of the control panel. After age is entered, the arrow will direct you automatically to enter the height.

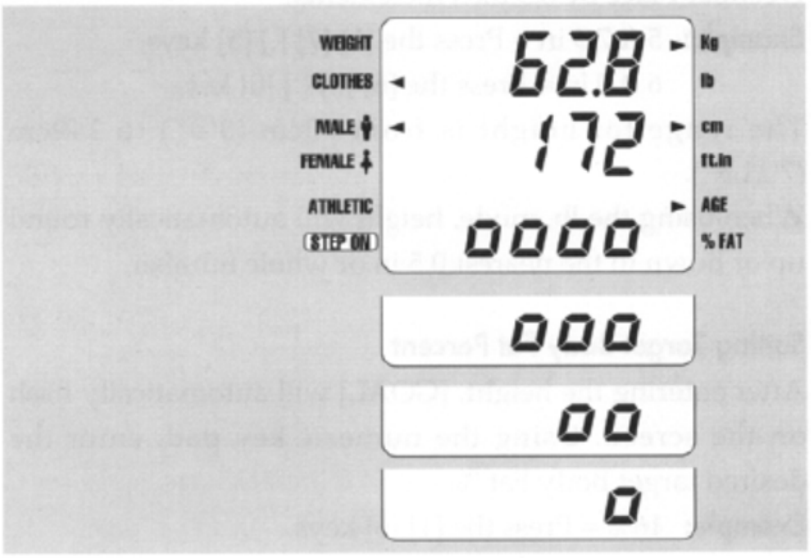
Enter height in cm. For example, for 172 cm, press the [1] [7] [2] keys.



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 the scale.

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 DEFIBBRILLATOR 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

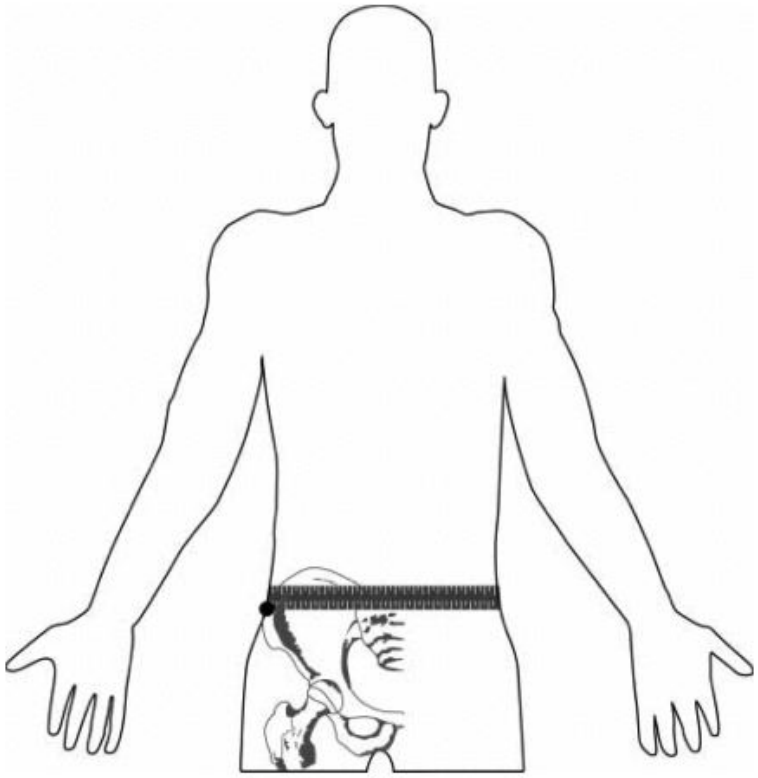
To define the level at which the abdominal circumference is measured, first locate and mark a specific bony landmark, the lateral border of the ilium. Have the participant stand and hold their shirt above the waist. Lower the pants and underclothing of the participant slightly, and standing behind and 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

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/QUALITY CONTROL

a. Calibration Procedures and Equipment Check

The Tanita scale is 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 record the weight indicated on the LED in the daily log. If the calibration weight is less than 8.5 kg or more than 11.5 kg, use the back-up scale, and notify the clinic coordinator to have the scale recalibrated by the manufacturer or by the appropriate institution personnel. 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

Field center technicians or examiners are centrally trained in all anthropometric measures. Technicians who cannot attend the central training can be trained and certified locally by the chief anthropometry technician. Each technician performs a minimum of 5 observed procedures to receive certification, with a level of agreement of measurements relative to the supervisor as specified in the QA/QC manual.

Technicians are observed by the study coordinator twice monthly for the first month, and then quarterly, to ensure standardization. The Supervisor Checklist is used to document these observations and deviations from the protocol are reviewed with the technicians. A minimum of 4 procedures every month is required in order to maintain certification.

10. COGNITIVE FUNCTION

10.1 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 I 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 mental status, memory, language, and executive function/processing speed, and olfaction. Test scores will be compared to age, education, and race-specific normative data to identify those with suspected dementia or MCI. Participants meeting a priori criteria for poor cognitive performance at Visit 5 and those who have significant cognitive decline from prior exams will be invited to a Stage II evaluation (see below.) The criteria for defining dementia/MCI at Visit 6 including consideration of significant change (decline) in cognitive functioning required for a diagnosis of dementia/MC, are detailed in MOP 17.

10.2 ADMINISTRATION – OVERVIEW

The order of test administration is as follows: MMSE, DWRT (exposure), DSST, DWRT (recall), Incidental Learning, FAS, Animal Naming, Trails A, Trails B, a 5-minute break, Logical Memory I, Digit Span (backwards), Boston Naming Test, Smell Test, and Logical Memory II. A brief description, and instructions for the administration and scoring of each measure are provided below. Administration of the complete battery requires approximately 45 minutes. A list of the test materials and detailed testing procedures are found in the QxQ instructions.

To avoid the influence of fatigue on the test results the cognitive battery is administered in the morning following the snack, through just after lunch. If this is not possible, this battery is administered early in the flow of the examination procedures, but not while the participant is fasting. 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 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 II may be determined in

CDART as soon as the test results are entered. Stage II selection may be determined before the participant leaves the clinic or afterwards, depending on the field center's data entry preferences.

10.3 MINI-MENTAL STATE EXAMINATION (MMSE)

a. Rationale

The MMSE was developed as a brief, standardized instrument for screening a limited number of cognitive functions. Since its introduction the MMSE has been utilized as a screening tool for the detection of cognitive impairment in institutionalized and community-dwelling individuals and as a device for tracking cognitive changes over time.

A number of variations with regard to administration, wording, and content of specific questions on the MMSE exist. The format utilized in this study includes the following modifications: Consistent with the CERAD battery participants will be requested to spell the word WORLD backwards for the attention and calculation component of the MMSE. As in the procedures utilized by CERAD and the Cardiovascular Health Study, participants will be assisted with spelling WORLD forward if they are unable to do so independently.

As recommended by Tombaugh and McIntyre, participants will be asked to name the county in which they reside, rather than the county in which the examination is taking place. Participants will be examined in different settings (clinic, home, and nursing home) and field centers. Therefore, specific place and floor of the building are modified to: "What is the name of the place where we are right now" and "Are we on the ground floor or a higher floor of this building?"

b. Administration

The MMSE is administered by interview and should be attempted on all participants. A detailed script is provided for each item and task. Each item response is entered into CDART, which calculates a total score (range 0-30).

10.4 DELAYED WORD RECALL TEST (DWRT)

a. Rationale

The DWRT is a measure of verbal memory that requires the participant to recall a list of 10 common nouns following a short delay. The DWRT was previously administered to all ARIC participants at Visits 2, 4 and 5 to a large subset of the participants at Visit 3 in Forsyth County, NC and Jackson, MS who had cerebral MRI scans. In addition, the DWRT was administered to a large subset of participants in the Carotid and Brain MRI ancillary studies.

b. Administration

The participant is presented with a stimulus card for each of 10 words. The examiner reads each word aloud, and asks the participant to repeat the word and use it in a sentence. This procedure is repeated, providing two exposures to the words. Following an approximate 5-minute delay, during which the (non-verbal) DSST is given, the participant is asked to recall as many words as possible.

Scores range from 0 to 10 words recalled.

10.5 DIGIT SYMBOL SUBSTITUTION TEST (DSST)

a. Rationale

The Digit Symbol Substitution Test (DSST) is a measure of psychomotor speed and sustained attention. Like the DWRT, the DSST has been administered in several previous ARIC exam visits (see DWRT for specific visits). Besides its own value, the DSST also serves as a nonverbal distracter task, interposed between learning and recall for the DWRT above.

b. Administration

The participant is asked to translate numbers (1-9) to symbols using a key provided at the top of the test form. The participant is provided with a pencil (without an eraser). Instructions are provided in a deliberate and slow pace.

One point is given for each correctly drawn symbol completed within the 90-second time limit. Scores range from 0 - 93.

10.6 INCIDENTAL LEARNING

a. Rationale

The Incidental Learning Test was adapted from the WAIS-R NI and provides a non-verbal measure of recent memory.

b. Administration

Following the DSST, the participant is presented with the Incidental Learning Template. The participant is asked to write down as many of the DSST symbols as he/she can remember, in any order. Next, the participant is asked to write down the number that was paired with each of the symbols from the DSST.

The test yields two scores: 1) Free Recall: total number of symbols recalled, regardless of pairing and 2) Pairing: number of correct symbols correctly paired with corresponding numbers. Scores for each range from 0-9.

10.7 WORD FLUENCY (FAS)

a. Rationale

The Word Fluency Test is a measure of verbal functioning. Like the DWRT, the FAS Test has been administered in several previous ARIC visits (see FAS for specific visits).

b. Administration

In this task the participant is asked to produce as many words as possible that begin with the letters F, A, and S within a time limit of 60 seconds for each letter, avoiding proper nouns, variations, plurals, and repetitions.

The score is the total number of admissible words produced across letters.

10.8 ANIMAL NAMING

a. Rationale

Animal Naming is a measure of category fluency (semantic association). Category fluency, and specifically animal naming, is part of the Boston Diagnostic Aphasia Examination, the Stanford-Binet test, and the CERAD.

b. Administration

The participant is asked to name as many different animals as possible within a 60 second time limit.

The score is given as the sum of all admissible names.

10.9 TRAIL MAKING TEST (TMT) A & B

a. Rationale

The TMT is a timed task in which participants connect letters and numbers in sequence as quickly as possible. TMT measures attention, sequencing, mental flexibility, and visual search and motor function.

b. Administration

In TMT A, the participant is asked to draw a line and connect a series of numbers (from 1-25) as quickly as possible. In TMT B, the participant is asked to draw a line and connect a series of numbers and letters, alternating between a given number and letter (e.g., 1 to A, A to 2, 2 to B, B to 3, etc.) as quickly as possible. Prior to each test part, the participant is given a sample test to demonstrate the task.

The score for TMT A and B is the number of seconds required to complete the task. A maximum of 240 seconds (4 minutes) and 5 errors are allowed.

10.10 LOGICAL MEMORY I AND II

a. Rationale

This test, part of the Wechsler Memory Scale-Revised version, provides a measure of immediate and delayed verbal recall for the number of ideas presented in two stories which are read to the participant.

b. Administration

Two stories are read to the participant, each at a slow and deliberate pace. After each story is presented, the participant is asked to recall as much of the story as possible. The Logical Memory I score provides a measure of immediate recall and is calculated as the average number of ideas recalled from Story A and B. Each story contains 25 scoring units, the maximum score is 25 (25+25/2).

An approximate 20 minute delay follows, during which the remaining (non-memory) tests are administered. Following the delay period, the participant is again asked to recall the stories. The Logical Memory II score provides a measure of delayed recall and is calculated as the average number of story elements recalled from Story A and B. As each story contains 25 scoring units, the maximum score is 25 (25+25/2).

10.11 DIGIT SPAN BACKWARDS

a. Rationale

Digit Span Backwards is part of the Wechsler Memory Scale-Revised and provides a measure of attention and working memory.

b. Administration

The participant is read a series of numbers progressively increasing in length from two to eight digits. After the numbers are read, the participant is asked to repeat the numbers in the reverse order. Two trials at each digit length are performed (i.e, 2 trials with 2 digits, 2 trials with 3 digits, etc.). The test is discontinued after two consecutive errors of the same length item.

Scores range from 0 – 12.

10.12 BOSTON NAMING TEST (BNT)

a. Rationale

The BNT assess visual naming ability using black-and-white drawings of common objects. For this study, the 30-item version used by the National Alzheimer's Coordinating Centers Uniform Data Set will be used.

b. Administration

The participant is presented with a series of line drawings of objects and asked to name each object. The items become progressive more difficult based on their frequency of occurrence in the English language.

A total score is calculated as the number of spontaneously produced correct responses. Scores may range from 0 – 30.

10.13 SMELL TEST

a. Rationale

Smell loss is prevalent among patients with Alzheimer's and Parkinson's disease and may be an early marker of neurodegenerative change. As at V5, olfactory function will be assessed using the Brief Smell Identification Test.

b. Administration

The participant is presented with 12 different pens containing odors which they are asked to identify in a multiple choice format.

A total score for number of odors correctly identified is calculated. Scores range from 0 – 12.

10.14 STAGE II – COGNITIVE STATUS

a. Rationale and Selection to Stage II

Participants who meet a priori criteria of poor cognitive performance at Visit 6 (i.e., who have either a low score on the MMSE or who score poorly in any cognitive domain and show significant cognitive decline from Visit 5) are invited to a Stage II evaluation, which consists of the CDR informant interview, to quantify the participant's functional status, and the Neuropsychiatric Inventory to characterize any neuropsychiatric symptoms. Eligibility for Stage 2 is determined by the selection algorithm programmed in CDART, based on information collected using the NCS form.

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 CDR interview. Each of the measures described below 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.

c. Clinical Dementia Rating (CDR)

The CDR scale includes the CDR Participant and the CDR Informant interviews, and two scores: the standard CDR summary score and the standard CDR sum-of-boxes. Since subject and informant responses must be recorded in categories of severity which unavoidably require subjective judgment, interviewers need good training and adequate QA to assure adequate standardization. The CDR gives important information about daily functioning, and it is a required element in the determination as to whether an individual is demented or has mild cognitive impairment, or is normal. The CDP is administered to all participants as part of stage 1, so is described in MOP 2. This form (CDP) will need to be referred to, along with the CDI, when the CDR scoring is being completed (on the CDS form). Because some subjective assessments are needed in order to make the CDR scoring determinations, only staff members who have experience in neurocognitive testing, who have previously undergone CDR certification, or who have a nursing degree would be considered for CDR certification.

d. Administration: CDR Informant

The CDR Informant form is administered by a certified staff member while an informant, usually identified by the participant, is seated, in a quiet private area without the subject present, whether in the clinic or at home, LTC facility. No equipment is required for administration. In the event that the informant does not accompany the subject in person to stage 2, the CDR informant can be administered by the study nurse over the telephone, as is standard for this portion of the CDR; this generally shortens the duration of the clinic visit.

e. Administration: CDR summary score

The certified staff member will score the CDR after completion of these two components (participant (CDP) and informant (CDI)), and will not score them in the presence of the subject or informant. A scoring algorithm will be taught to study staff based on the responses to the questions on both the CDR subject and the CDR informant; this will be completed in the event of a missing informant, as well.

The study staff member will be primarily responsible for generating the CDR box scores, ranging from 0 (normal) to X (severe impairment) for each of the following 6 areas, for the standard CDR: memory (M), orientation (O), judgment and problem solving (JPS), community affairs (CA), home and hobbies (HH), and personal care (PC).

The online training module described above teaches how to translate a participant's responses into box scores, with the following basic guidelines: 0=no impairment; 0.5= questionable impairment; 1= mild impairment; 2= moderate impairment; X=severe impairment. The standard CDR sum-of-boxes is simply a sum of the first 6 CDR box scores (with total possible range from 0 to 18). The standard Global CDR is calculated based on a formula generated at Washington University, where the CDR online training is administered. This standard Global CDR will only be used for publication purposes and will not be part of the classification or selection process. This website: http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html generates a global CDR score based on individual box scores, and the same formula used to generate scores from this website are used to generate Global CDR scores based on box scores in the ARIC-NCS study.

The basic formula to generate a global CDR score is as follows: memory is considered the primary category, with others considered secondary. The global CDR is the same as the M score if at least X secondary categories are given the same score as M; however, if X or more secondary

categories have a score greater or less than the M score, the global CDR score equals the score of the majority of secondary categories on whichever side (scores below or scores above) of M has the greater number of secondary categories. If three of these secondary categories are scored on one side (below or above) of M and two are on the other side of M, CDR=M. When the M score is 0.5 (or greater); the global CDR cannot be 0. Instead, when M=0.5, the global CDR can be 1 if X or more of the other categories are scored at a 1 or greater. I M=0, the global CDR=0 unless there is a score of 0.5 or greater in two or more secondary categories (in which case CDR=0.5).

f. Administration: Functional Assessment Questionnaire (FAQ) Score

Although the Functional Assessment Questionnaire (FAQ) score is not administered as a distinct scale, the items for the FAQ are embedded within the CDR, and scoring ranges from a 0 (normal function) to 1 (has difficulty, but does by self), to 2 (requires assistance, to an FAQ of X (dependent), depending on the specific response. There are 9 items from the CDR which are also FAQ questions (there are 10 FAQ questions; one CDR question encompasses two FAQ questions). The following items on CDR are used for the FAQ: CDR informant items 17, 18, 22, 25, 26, X1, X5 (scored twice: covers two FAQ questions), X6, and X7. The total FAQ score, used for classification, is the sum of the 10 individual scores.

g. Quality Assurance

Online training and certification for the CDR is required (www.adrc.wustl.edu). After selecting "Begin CDR Training", the user will be asked to register after which they will have access to 9 videos, each approximately X0 minutes in duration. The trainee should plan to review these videos over several days. Two audio-taped recordings of the CDR interviews (Informant and Subject interviews) per trainee will be reviewed by a study neurologist for certification.

During the first 6 months of the study, 2 audiotaped sessions of the CDR interviews (CDR-Subject [CDP]; CDR-Informant CDI]) and associated documentation (PDF file from DMS for CDP, CDI, and CDR-Summary [CDS]), for each interviewer will be reviewed by a neurologic expert. General feedback that pertains to all examiners will be provided on QC Committee conference calls. These calls will also provide an opportunity to discuss and problem-solve various exam issues that may arise.

h. Rationale: Neuropsychiatric Inventory (NPI)

The NPI consists of questions relating to personality and behavioral changes. Certain types of dementia (such as frontotemporal dementia) may be more likely based on the presence or absence of some of these behavioral changes, or the presence of significant depression in combination with a high CES-D score might increase the likelihood that apparent memory or other cognitive problems are actually due to depression, rather than dementia.

i. Administration: NPI

This scale is completed after the CDR with the informant (CDI) only, and is done with the informant, seated, in a quiet private space (either in clinic or at home, or by telephone, depending on the remainder of the visit). The participant should not be present. No special equipment is needed.

j. Quality Assurance

Certification and recertification are performed as described above. The NPI should be audio recorded with the CDI.

10.15 REFUSALS AND DISCONTINUED TESTS

On occasion a test will not be performed or discontinued. The reasons may include participant refusal, task difficulty, or if the examiner determines that the participant is unable to perform a test due to a physical impairment. These circumstances are described in detail in the QxQ.

10.16 TRAINING, CERTIFICATION, AND QUALITY CONTROL

Prior to the examination, examiners will be trained centrally to a common level of proficiency in the administration and scoring of the neurocognitive measures. Following central training, examiners will upload audio-taped neurocognitive assessments on age-eligible volunteers (the measures are found in the NCS cognitive testing packet) and associated paper forms to a secure location on the ARIC website for review by an investigator on the Neurocognitive Committee. Certification assessments are not performed on ARIC participants. Examiner certification for the neurocognitive exam is achieved by review and approval of performance by the neurocognitive expert. Following central training (1) New examiners will submit 3 audio-taped neurocognitive assessments (and associated scoring materials) for review; (2) Examiners who were previously certified to perform the neurocognitive assessment during Visit 5 will submit 1 audio-taped assessment for review.

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

Maintaining proficiency in the administration of the neurocognitive measures requires regular exposure to the protocol. In order to maintain certification, primary examiners will administer the neurocognitive measures at least 4 times per month.

a. Audio-recording of Neurocognitive Component of Interview.

Audio-taped sessions and associated documentation for each examiner should be submitted for central review by a neurocognitive expert to ensure appropriate pacing, adherence to protocol, and accuracy of recorded responses. Notes about any inconsistencies will be relayed to the study coordinator. The schedule for QC recordings is as follows: 2 in the first month of the study followed by 1 recording every other month thereafter until the end of the study. General feedback that pertains to all examiners will be provided on Quality Assurance and Control Committee conference calls. These calls will also provide an opportunity to discuss and problem-solve various exam issues that may arise.

11. Hearing Assessments

Overview

This component of the Visit 6 examination collects information on self-reported hearing loss, pure tone audiometry, speech-in-noise perception, and tympanometry testing. The examination is conducted in a sound-treated booth at each ARIC field center, and/or with home-based testing equipment for those who are unable to travel. At the field center participants complete two questionnaires and a complete audiometric test battery. In the home, participants complete two questionnaires but only a portion of the audiometric test battery. The scientific aims are to investigate factors that lead to hearing loss and to study the influence of quantitative and qualitative assessments of hearing abilities and on the cognitive and physical functioning of older adults. The examination is described in detail in the Hearing Assessment Procedures Manual (ARIC Manual 22), available at https://www2.cscc.unc.edu/aric/aric-ncs-forms-and-qxqs

The interviewer-administered questionnaires are the Self-Reported Hearing and Noise Exposure (HNE) and the Hearing Handicap Inventory for the Elderly-Screening (HHI), which are administered prior to the otoscopy and the audiometry. A visual examination of the outer ear follows, including the auricle, ear canal, and eardrum is conducted by standardized otoscopy. The presence of cerumen or other problems that may interfere with audiometric testing are noted and will drive the selection of the ear transducer (insert earphones or headphones).

Pure tone air conduction audiometry is used to determine the participant's hearing thresholds at frequencies across the range of human hearing (250-8000 Hz). Pure tone signals of varying intensities are presented to the ear through insert earphones and the participant responds to the signal by pressing a response button or raising their hand (in the home-based exam). The audiometric threshold is defined as the lowest intensity at which the participant is able to detect the signal 50% of the time on an ascending run using the Manual Hughson Westlake procedure. Testing is conducted in a sound-treated booth using the Equinox 2.0 Diagnostic Audiometer in the clinic or in a quiet room using the ShoeBox portable audiometer in the home-based visit. Speech-in-noise testing (QuickSIN) measures a participant's ability to understand speech in the presence of varying levels of background noise. Lastly, tympanometry as a measure of middle ear function is performed only if time permits.

Equipment functional inspection is performed daily, bio-acoustic equipment calibration is monitored weekly, and equipment is professionally calibrated yearly by the local Interacoustics distributor. The TDH Headphones that accompany the portable audiometer are calibrated annually by Clearwater Clinical Mobile Health Devices. Distributors also professionally evaluate the sound environment annually.

12. INTERVIEWS

12.1 OVERVIEW

As in previous examinations of the ARIC cohort a set of standardized questionnaires is administered by trained and certified interviewers who follow a common protocol throughout the study. 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. The cognitive battery interviews are always administered following the snack as close as possible. 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. For this purpose the interviews have been grouped as blocks A through C.

Block A Interviews

12.2 NEUROLOGIC HISTORY

a. Rationale

The Neurologic History (NHX) includes basic questions about past neurologic diagnoses as well as past head trauma. This information is important in identifying individuals who might be excluded from subsequent analyses, or identifying participants who might warrant further evaluation in later ancillary studies. It also provides useful information about some symptoms that are specifically associated with Parkinson's disease, in order to identify participants who might have Parkinsonism and not carry a diagnosis of Parkinson's.

b. Administration

The NHX is administered to all participants at Visit 6, by a staff member in a quiet room. No specific equipment is required for this interview.

c. Training and Certification

ARIC staff is trained centrally or locally. Certification is achieved by the demonstration of adequate technique on 5 interviews, reviewed and approved by the study coordinator or interviewer supervisor.

d. Quality Assurance

Two audio-recorded interviews per technician is reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee.

12.3 EPWORTH SLEEPINESS SCALE

a. Rationale

The Epworth Sleepiness Scale (ESS) is a measure of daytime sleepiness, and was previously administered to the ARIC participants who were also in the Sleep Heart Health Study. It is used to identify individuals with likely sleep disturbances, and will allow evaluation of sleep disturbances both as a cause and as an effect of possible cognitive problems in ARIC participants.

b. Administration

The ESS is administered to all participants at Visit 6, by a staff member in a quiet room. No specific equipment is required for this interview

c. Training and Certification

ARIC staff is trained centrally or locally. Certification is achieved by the demonstration of adequate technique on 5 interviews, reviewed and approved by the study coordinator or interviewer supervisor.

d. Quality Assurance

Two audio-recorded interviews per technician is reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee.

12.4 CLINICAL DEMENTIA RATING SCALE (CDR)

a. Rationale

The CDR gives important information about daily functioning, and is a required element in the determination as to whether an individual is demented or has mild cognitive impairment, or is normal. The CDR includes two parts: the CDR Participant (CDP) and CDR Informant (CDI) interviews. The CDR Participant (the portion of the CDR administered to the participant) is administered to all participants examined at the field center or home at Visit 6, and thus is described below. Details about the administration and scoring of the CDI and the CDS (the form where summary scores are entered) are found in MOP 17 (the CDI/CDS is only completed for participants meeting cognitive criteria for stage II).

b. Administration

The CDP form is administered by a certified staff member to the participant while the participant is seated, and requires no equipment for administration. It should be administered in a quiet private area.

c. Scoring

The CDR scale includes the CDR Informant and CDR Participant interviews, and two scores: the standard CDR summary score and the standard CDR sum-of-boxes. Scoring for the CDS should be completed after both the CDP and CDI are completed.

d. Training and Certification

Since subject and informant responses must be recorded in categories of severity which unavoidably require subjective judgment, interviewers need good training and adequate quality assurance support for adequate standardization. Prior to the examination examiners are trained centrally to a common level of proficiency in the administration and scoring of the instruments. Following central training, examiners will upload audio-taped assessments on age-eligible volunteers to a secure location on the ARIC website for review by an investigator on the Neurocognitive Committee. Certification assessments are not performed on ARIC participants.

Examiner certification is achieved by review and approval of performance by the neurocognitive expert. Following central training (1) New examiners will submit 3 audio-taped neurocognitive assessments (and associated scoring materials) for review; (2) Examiners who were previously certified to perform the neurocognitive assessment during Visit 5 will submit 1 audio-taped assessment for review.

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

Block B Interviews

12. 5 PERSONAL HISTORY

a. Rationale

The Personal History Questionnaire (PHX) helps to characterize the socio-economic characteristics of the study participant at the level of the household and in terms of perceived socio-economic status.

b. Administration

The Personal History is interviewer-administered and can be administered at any time during the visit. Staff must be aware of the potentially sensitive nature of disclosing one's income and self-rated social status. To avoid disclosing income figures having to verbalize statements that may carry some degree of social stigma, response cards are used. It is important that staff maintain a calm and neutral tone of voice, and present the response cards for questions 1 and 3 to the participant as they clearly enunciate the questions. Detailed instructions for administering each question are provided in the question by question instructions.

c. Training and certification

ARIC staff is trained centrally or locally. Certification is achieved by the demonstration of adequate technique on 5 interviews, reviewed and approved by the study coordinator or interviewer supervisor.

d. Quality Assurance

Two audio-recorded interviews per technician are reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee.

12.6 MEDICATION SURVEY

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 Coordinating Center).

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 it can be interrogated by the ARIC technician for medications that exclude a participant from 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

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

h. Certification

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

- The candidate is trained by the lead certified interviewer at the corresponding Field Center.
- The candidate has completed five taped interviews demonstrating adequate technique based on review and approval by the lead interviewer.
- The Study Coordinator has submitted a request for certification to the Coordinating Center on behalf of the candidate.
- The Coordinating Center has sent to the Study Coordinator a mock medication bag with detailed instructions for the candidate's certification.
- The candidate independently completes an MSR and enters it into the Data Management System.
- The Study Coordinator returns the medication bag with all of its contents, the instructions, and printouts of the MSR screens to the Coordinating Center for evaluation.
- The candidate passes with a score of ≥ 80%.

i. Quality Assurance

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

j. 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) are listed alphabetically in hard copy. Details of data collection are provided in the Question-by-Question instructions for the MSR.

12.7 SMOKING AND ALCOHOL USE FORM

a. Rationale

The Smoking and Alcohol Use Form is completed during the interview portion of the Visit 6 cohort 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

Current cigarette use is ascertained, not including cigars, pipes, or other forms of tobacco consumption. Frequency of alcohol consumption is determined as usual weekly intake, specifying the serving sizes for beer, wine and hard liquor. 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.

d. Quality Assurance

Monthly data quality reports will be prepared by the Coordinating Center and reviewed by the Quality Control Committee examining the frequency of out-of-range values, missing data, and summary statistics by field center and interviewer.

12.8 SF-12TM GENERAL HEALTH

a. Rationale

The 12-item Short-Form Health Survey, SF-12, is a shortened version of the SF-36 Health Survey (Ware, Kosinsk, and Keller, 1995, 1996) which assesses health-related quality of life. Like the SF-36, it is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is the most widely-used health survey throughout the world because it is both brief and comprehensive, readily available, psychometrically-sound, and of proven usefulness in measuring health status and monitoring health outcomes. However, the SF-36 has been judged to be too long for the ARIC examination. The ARIC study will be using a shortened version of the SF-36. The same eight domains of health that can be estimated from the SF-36 can be constructed using the SF-12v2, but estimation of the physical and mental health domains have the greatest accuracy. All of the questions and response categories on the SF-12 Version 2 are identical to those on the SF-36. The questionnaire is available in the standard (4-week) and acute (1-week) recall versions – ARIC will use the standard version. The SF-12v2 was chosen for ARIC because (1) it has been demonstrated to have reproducibility and validity compared with other health-related quality of life (HR-QOL) forms, and (2) U.S. population norms exist.

b. Equipment and Setting

The interview takes place in a quiet and private setting to put the participant at ease and allow the participant to focus on the task. Data are collected electronically using the DMS. A paper version of the form is available for back-up if the DMS is unavailable. The SF-12v2 items are scored so that a higher score indicates a better health state. The algorithms for scoring the summary physical

[Physical Component Summary (PCS-12)] and mental [Mental Component Summary (MCS-12)] health scores are documented in Chapter 8 of the manual (How to Score Version 2 of the SF-12™ Health Survey, 2002). In addition to estimates of PCS and MCS, the manual provides scoring algorithms for the eight domains of health profiled by the SF-36.

c. Training and Certification

Interviewers are trained and certified in general interviewing techniques and administration of the form. This requires familiarity with the contents and procedures for administering the SF-12v2 form via the DMS or on paper. Staff can be trained centrally or locally at the field center. Retraining is required if quality assurance analyses indicate poor performance or inconsistent results.

d. Quality Assurance

Monthly data quality reports will be prepared by the Coordinating Center and reviewed by the Quality Control Committee examining the frequency of out-of-range values, missing data, and summary measures (PCS, MCS) by field center and interviewer.

12.9 CENTER FOR EPIDEMIOLOGIC STUDIES DEPRESSION SCALE (CESD) SHORT FORM & HOPELESSNESS

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 6, 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. A related construct, hopelessness, has been independently associated with increased risk of incident MI, cancer, and all-cause mortality (Everson et. al, 1996). One item assessing hopelessness will be collected.

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. Hopelessness is simply the corresponding score to question #12.

d. Training and Certification

Interviewers are centrally trained. Study coordinators are responsible for training new staff if necessary after central training based on standardized interviewing techniques, QxQ instructions, and role playing example situations.

e. Quality Assurance

Data quality is monitored by the Quality Control Committee, based on analyses prepared by the coordinating center. In cases where score patterns suggest suboptimal data quality, the study coordinator will be notified and technical assistance and remedial action provided. In addition, interviews will be audio-taped and regularly reviewed for adherence to protocol.

f. 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.

g. 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.

12.10. DIABETES QUESTIONNAIRE (DQF)

a. Rationale

The first section of this instrument is administered to all participants, at the field center or home examination, since it addresses general preventive care practices, family history of diabetes and a physician diagnosis of diabetes if not previously identified in ARIC. Participants who have diabetes are then asked questions about their history of diabetes, preventive care practices applicable to diabetes, and an assessment of hypoglycemia.

b. Administration

The diabetes questionnaire is interviewer administered.

c. Training and Certification

ARIC staff is trained centrally or locally. Certification is achieved by the demonstration of adequate technique on 5 interviews, reviewed and approved by the study coordinator or interviewer supervisor.

d. Quality Assurance

Two audio-recorded interviews per technician is reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee.

12.11 DIABETES TREATMENT SATISFACTION

a. Rationale

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) is commonly used to measure patient satisfaction with diabetes treatment. This instrument is used under license. Treatment satisfaction is assessed on a six-items scale, and two items record the perceived frequency of hyperglycemia and hypoglycemia.

b. Administration

The DTS is interviewer-administered in ARIC, with the use of a response card to help orient the interviewee to the six item scale.

c. Training and Certification

ARIC staff is trained centrally or locally. Certification is achieved by the demonstration of adequate technique on 5 interviews, reviewed and approved by the study coordinator or interviewer supervisor.

d. Quality Assurance

Two audio-recorded interviews per technician is reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee.

Block C Interviews

12.12 PHYSICAL ABILITY QUESTIONNAIRE

a. Rationale

This Physical Ability Questionnaire (PAQ) was designed to ascertain participants' ability to function independently, without the help of other persons or without the aid of special equipment. The questionnaire includes elements from the Katz Index of Independence in Activities of Daily Living (Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., & Jaffe M. W. (1963). Studies of illness in the aged: The index of ADL: A standardized measure of biological and psychosocial function. JAMA, 185(12), 94–99.) and the Lawton Instrumental activities of Daily Living Scale. (Lawton, M.P., and Brody, E.M. "Assessment of older people: Self-maintaining and instrumental activities of daily living." Gerontologist 9:179-186, (1969).)

b. Administration

The PAQ is administered at the time of the Visit 6 during the field center examination. Each question within the PAQ has several response options which are read out loud to the participants following the question. For ease of administration, participants are provided with a card containing the response options. Physical ability is assessed in the absence of special equipment. Examples of special equipment include canes, walkers, lift chairs, motorized beds. If the device is used to aid in physical mobility, e.g. walking, balance, transferring in and out of bed or chairs, it is considered special equipment.

c. Training and Certification

ARIC staff is trained centrally or locally. Certification is achieved by the demonstration of adequate technique on 5 interviews, reviewed and approved by the study coordinator or interviewer supervisor.

d. Scoring

No specific scoring protocols are available for this questionnaire

e. Quality Assurance

Adherence to protocol is monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee.

12.13 PHYSICAL ACTIVITY

Information on habitual work and leisure-time related physical activity is collected by means of the questionnaire previously used in ARIC's Visit 1, Visit 3, and Visit 5. 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.

Visit 6 adds questions on physical activity within the household and transportation domain. 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 question by question 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 Coordinating Center, 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

Interviewers are centrally trained prior to the start of the study. Topics include proper coding of physical activities, usage of response cards, scoring and knowledge of when and how to probe.

e. Certification

Manual 12 on Quality Control, describes the certification procedures.

f. Quality Control

The data collected by each interviewer are periodically reviewed by the Quality Control Committee from quality control analyses performed by the Coordinating Center. Data patterns suggestive of deviations from protocol are brought to the attention of the field center principal investigator and project manager. Observation of the interviews or review of taped interviews the follows, with discussion of possible remedial actions with staff. Major deviations are brought to the attention of the Executive Committee.

g. Data Collection

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

12.13 HEARING HANDICAP INVENTORY

a. Rationale

The purpose of this standardized scale is to identify the degree of difficulty a study participant may experience on account of hearing loss.

b. Administration

The questionnaire should be administered in a quiet room with minimal ambient noise. Participants should be encouraged to use any listening devices they may own or rely on. *Since* participant motivation and level of understanding can have a significant impact on performance and length of time required for administration, the questionnaire should be administered strictly according to the protocol.

c. Scoring

N.A.

d. Training and Certification

Prior to administering the Hearing Handicap Inventory for the Elderly-Screening (HHI) Form, all examiners are certified by attending central training.

e. Quality Assurance

Certification in HHI form administration is maintained by completing at least four sessions per month and completing quarterly review sessions with training team.

12.14 SELF-REPORTED HEARING AND NOISE EXPOSURE FORM

a. Rationale

The purpose of this standardized interview is to assess self-reported impairment, the occurrence of tinnitus, prior exposure to loud noise in different settings, and the use of hearing aids.

b. Administration

The questionnaire should be administered in a quiet room with minimal ambient noise. Participants should be encouraged to use any listening devices they may own or rely on. Since participant motivation and level of understanding can have a significant impact on performance and length of time required for administration, it is important that the questionnaire be administered according to protocol.

c. Scoring

N.A.

d. Training and Certification

Prior to administering the Self-Reported Hearing and Noise Exposure (HNE) Form, all examiners are certified by attending central training.

e. Quality Assurance

Certification in HNE form administration is maintained by completing at least four sessions per month and completing quarterly review sessions with training team.

13. SITTING BLOOD PRESSURE

13.1 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 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.

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 13.1 OMRON HEM907XL sphygmomanometer and 4 cuffs

OMRON HEM907XL with four cuffs

13.2 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.

13.3 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 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 participants 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 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 along side 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 12.1. (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 12.1

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 minutes 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 13.2: 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 13.3). 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 13.3

13.4 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 13.4) and AC sign (Figure 13.5) is visible in the lower window.

Figure 13.4

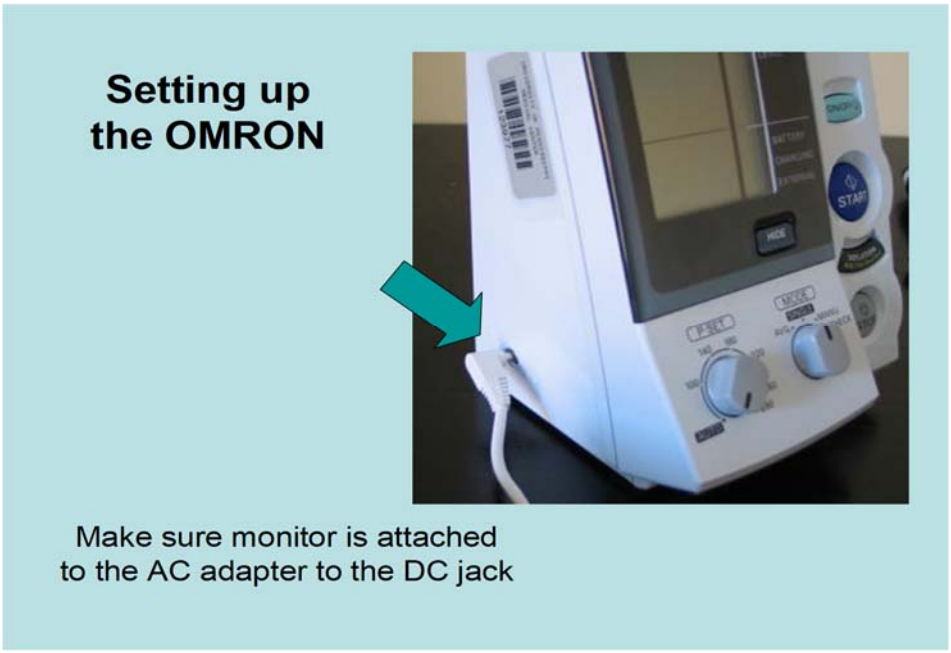


Figure 13.5

When the power is OFF, push the ON/OFF (power) button for more then 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 13.6). If needed push the DEFLATION (deflation control)/Measurement Result Display Switch Button to change the set value to 3 inflations.

Figure 13.6

Push the START button and F2 function is displayed in the first window and 0 waiting time is displayed in the middle window (Figure 13.7)

Figure 13.7

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 13.8).

Figure 13.8

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

Table 12.2 summarizes the needed settings for the exam

Table 12.2

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 13.9).

Figure 19.9

AUTO AVG

Next, connect the air tube to the cuff (Figure 13.10).

Figure 13.10

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 13.2.7, 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 13.11).

Figure 13.11

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 13.12 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 13.12

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 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

13.5 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 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC 8).

As a participant safety procedure, if the average blood pressure is equal to or greater than 200 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 5 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 the DMS instead of the first set. If the average blood pressure still 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 visit to his/her provider of care during the same day, or arranges transportation to the nearest emergency room for a medical evaluation of the participant's blood pressure. Section 26 of this manual of operations describes the procedures used to report study results.

13.6 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.
-

13.7 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.

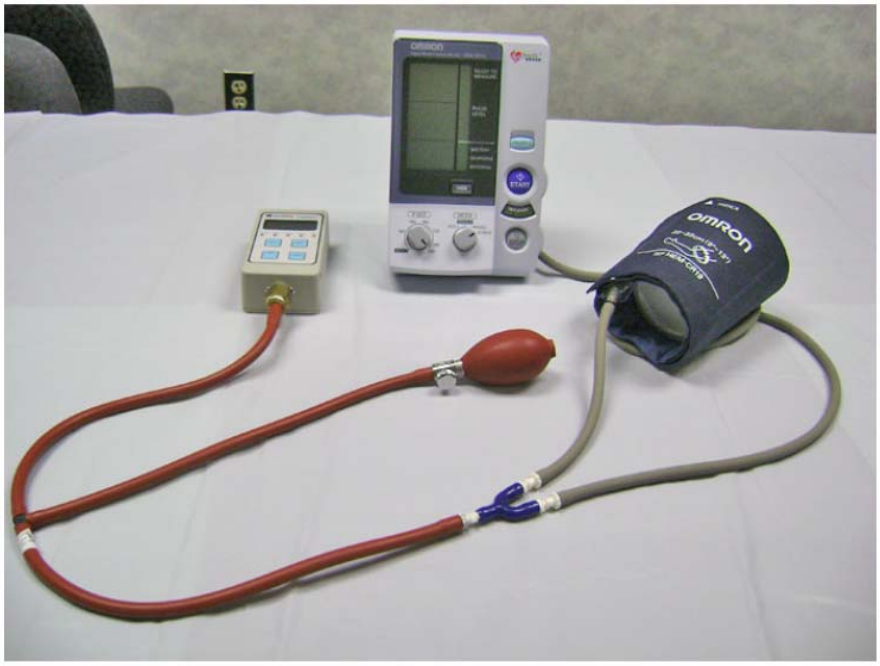
b. Quarterly Validation of the OMRON Sphygmomanometer

Each OMRON unit is checked every 3months 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 Coordinating Center for inclusion in the quality control reports. A copy of the calibration log is found in the Appendix 13.

Equipment Required for Accuracy Check

The calibration equipment is the Pressure-Vacuum Meter (Shown in Figure 13.13). 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/NCS Quality Control Committee, once per year each DigiMano device is shipped to the manufacturer for calibration. Completion of this check by Netech is then reported to the Quality Control Committee.

Figure 13.13



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 calibration log (together with the unit number, the date and the technician ID) and send the log to the ARIC Coordinating Center. A copy of the calibration log is found in Appendix 13.

13.8 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.

14. PHYSICAL FUNCTION, UNINTENTIONAL WEIGHT LOSS AND ENDURANCE

14.1 OVERVIEW

This abbreviated objective measure of physical function is based on previous epidemiologic studies of aging, such as the Established Populations for Epidemiologic Studies of the Elderly (EPESE), Framingham Heart Study, the Cardiovascular Health Study, Women's Health and Aging Study, Health ABC, and the Baltimore Longitudinal Study of Aging, that incorporated physical function assessments. The battery described below includes the Short Physical Performance Battery (SPPB) which consists of chair stands, a usual-paced 4 meter walk, balance tests, and grip strength. Prior to training, all examiners should review the QxQ and complete the online training module for the National Institute on Aging SPPB at http://www.grc.nia.nih.gov/branches/ledb/sppb/index.htm. Note that the video does not include training on grip strength. This video should be reviewed prior to initial training session and every 6 months. Details on downloading the video can be found at this website by clicking "Instructions" - pdf. "CD (Download and Execute) – (exe)" contains the video material to be downloaded.

Existing studies have established bi-directional relationships between mobility and cognitive function,1-6 especially executive function7-14 and processing speed.13,15 Some studies have shown that cognitive impairments precede mobility decline,1,2 while others have demonstrated that impaired mobility precedes cognitive decline in older adults.3-5 To date, the relationship of cognition with mobility is poorly understood. ARIC and other studies have reported associations between cardiovascular risk factors and brain structural abnormalities that are also linked to cognitive and physical decline (i.e. functional decline). These risk factors are also associated with reduced cardiovascular fitness or endurance. In turn, endurance has been associated with brain structure and cognition in a small study.16 Cardiovascular endurance may suffer substantial decline prior to the development of recognizable cognitive- or mobility-related difficulty, particularly in sedentary or cognitively impaired individuals, and may be an early indicator of impending functional limitation. Implementing measures of endurance in the ARIC cohort will elucidate temporal relations of cognitive change from mid-life to late-life endurance and provide an opportunity to examine relations of late-life cardiovascular endurance with late-life cognitive outcomes in the ARIC-NCS cohort.

Although maximum treadmill-based testing with measured oxygen consumption is considered the "gold-standard" method for ascertaining endurance and cardiovascular fitness, this approach may be unsuitable for many older adults. With increasing age, the proportion of even apparently healthy ambulatory older persons who can satisfactorily complete a treadmill exercise test decreases markedly, from 30% in those aged 75 to 79 years, to 25% in persons aged 80 to 84 years, to 9% for those over 85 years.17 This is especially problematic in longitudinal studies of the aging process in which change in fitness and exercise capacity with age and disease progression are of great interest.

The American Thoracic Society's 6-Minute Walk Test is a widely accepted measure of submaximal level of functional capacity in clinical and research settings. Time constraints often limit its use in large studies. The Two Minute Walk is adapted from the 6-Minute Walk Test Protocol and is the recommended measure of sub-maximal cardiovascular endurance in the NIH Toolbox Endurance Domain.18 Validation and reliability studies of the Two Minute Walk have been reported in participants aged 3-85 years of age. The distances covered in the Two Minute Walk and the 6-minute walk are reliable between sessions (intraclass correlation coefficients = 0.888 and 0.917, respectively); the distances in the Two Minute Walk and 6-minute walk are highly correlated (r=0.968).10 The Two Minute Walk records the distance one is able to walk on a 50-foot course (out and back) in two minutes. The participant's raw score is the distance walked in two minutes, reported in feet. This score can be used as a raw measure or converted to the Toolbox normative scale scores. Studies indicate that approximately four minutes is required to complete the Two Minute Walk, including test instructions and practice.

Unintentional weight loss is an important risk factor in older adults that may be a marker of metabolic, psychiatric, neurologic, and other medical disorders, is associated with mortality, and is also considered a component in the frailty syndrome.19 Fifteen to twenty percent of adults 65 years or older have unintentional weight loss when followed five to ten years; rates are higher in nursing home residents.20 The most widely used definition of frailty defined involuntary weight loss as a loss of at least 10 pounds in the prior year or, at follow-up, of 5% of body weight in prior year by direct measurement of weight.19 Objective measures improve classification of weight loss compared to subjective reports of weight loss and will be available in the ARIC exam at visit 6. Objective assessments will be repeated using previous ARIC protocols; subjective reports will reflect methods used in the Cardiovascular Health Study.

14. 2 SHORT PHYSICAL PERFORMANCE BATTERY (SPPB)

A direct assessment of physical performance has become standard practice in epidemiologic observational studies of health and disease. The most commonly used assessments, such as the SPPB, were initially designed to differentiate function in older adults. The SPPB is a well-known and validated lower extremity performance measure that predicts adverse outcomes including mortality, falls, nursing home placement, and incident disability in older adults.

a. SPPB Administration Overview

Since motivation and level of understanding can have a significant impact on performance, each component of the exam should be administered strictly according to the protocol and in the following sequence:

- Explain the procedure to the study participant making sure to adhere to the script.
- Demonstrate the procedure, using the script.
- Ask the participant if he/she has any questions.
- Re-explain the procedure briefly using the script.

• Ask the participant to perform the procedure.
• Begin all timed procedures with the words, "Ready? Go!"

Use the script provided to assure that all key points are covered when you describe each test and how to perform it properly. Do not provide additional description or encouragement beyond the key points provided by the standard scripts.

Demonstrate each maneuver correctly. Experience has shown that participants follow more closely what the examiner does rather than what he/she says. If the participant indicates they do not understand the test maneuver, demonstrate it again rather than solely relying on repeating the verbal instructions.

Limit practice trials for each test to those described in the individual measurement procedures. Allow the participant to rest between tests if out of breath or fatigued during the assessments. If a test is not attempted because the participant refuses or cannot understand the instructions, record “Participant refused”. If you or the participant considers the test unsafe, record “Not attempted/unable” on the scoring form. If a test is attempted, but cannot be completed or scored, record “Attempted, unable” on the scoring form.

For the walking and balance tests, the examiner should stand next to and slightly behind the participant and position his/her hands very close to either side of the participant’s trunk at the hip or waist level without touching the participant. The examiner should be ready to place both hands on the participant to stabilize them if necessary. If the participant loses balance, the examiner should grab/catch the participant with both hands at the trunk to stabilize them. If the participant begins to fall, the examiner should reach under the participant’s shoulders from behind and slowly ease them down to the floor, rather than try to catch the participant while standing still. This strategy should protect both the participant and examiner from injury.

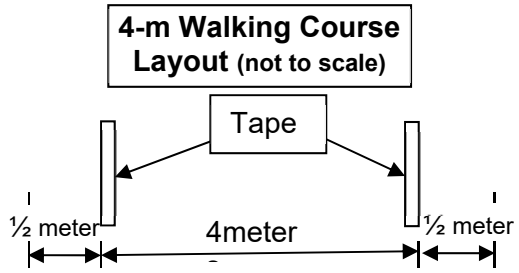
If the participant falls and is not injured, the examiner should have the participant get on their knees or on all fours, place a chair next to the participant, and have the participant support themselves on the chair as he/she helps lift the participant under the shoulders. The examiner should not try to lift the participant from the floor by him/herself.

• Footwear: To reduce effects of different footwear on test performance, the participant should wear tennis shoes or comfortable walking shoes with minimal or no heels. The participant may perform the tests in stocking or bare feet if appropriate footwear is not available.

• The chair should be a straight-backed chair without arms, with seat height of 45 cm. It should be placed on a non-skid surface (e.g., low pile carpeting if available) with the back of the chair against a wall for stability. There should be adequate room in front and on the sides of the chair for the examiner and participant to move freely.

• The standing balance test should be performed with the participant standing a little less than an arm's length from a wall to provide an additional source of support should loss of balance occur.

• Walking course: The short walks should be conducted on a 4-meter path laid-out in an uncarpeted, unobstructed, low traffic corridor at least 122 cm (about 4 feet) wide. The start and finish lines will be marked by tape on the floor. Allow an additional ½ meter on each end of the walking course.



• For grip strength, the participant should be seated at a standard height table at about shoulder level or next to a table with an adjustable tray table attached.

b. Equipment: SPPB

• Digital stopwatch (repeated chair stands, standing balance, short walk tests)

• Standard chair: straight back, flat, level, firm seat; seat height 45 cm at front (single and repeated chair stands).

• Colored tape to mark walking course (see drawing included in description of walking tests)

c. Safety Issues and Exclusions - SPPB Procedure

The large majority of participants should be able to attempt each performance test. Walking aids may not be used for the chair stand or standing balance tests but may be used for the timed 4-meter walks if participants cannot walk the distance without aids. Crutches, casts or other immobilizing devices alter the participant's usual mobility; if present, do not test the participant and note the reason test was not performed. Exclusion from any performance test is also based on examiner assessment or participant concerns that the test would be unsafe. In the latter case, the examiner should describe the test and discuss with the participant his/her specific concerns about attempting the test, including physical problems and known disabilities. The reason for not attempting a test, or inability to perform a test are recorded on the data form.

For the walking and balance tests the examiner stands next to, and slightly behind the participant and positions his/her hands very close to either side of the participant's trunk at the hip or waist level without touching the participant. The examiner should be ready to place both hands on the participant to stabilize them if necessary. If the participant loses balance, the examiner should catch the participant with both hands at the trunk to stabilize them. If the participant begins to fall, the

examiner should reach under the participant's shoulders from behind and slowly ease them down to the floor, rather than try to catch the participant while standing still. This strategy should protect both the participant and examiner from injury.

If the participant falls and is not injured, the examiner should have the participant get on their knees or on all fours, place a chair next to the participant, and have the participant support themselves on the chair as he/she helps to lift the participant under the shoulders. The examiner should not try to lift the participant from the floor by him/herself.

14.3 ADMINISTRATION OF THE SPPB SINGLE CHAIR STAND

This is a test of ability to stand up from a standard chair without using one's arms. This task is also used to screen for the ability to do repeated chair stands. Walking aids including canes may not be used. Although you will demonstrate the repeated chair stands, it is not necessary to demonstrate the chair stand for the single chair stand. Do, however, show the participant how to cross their arms on their chest.

The standard chair is placed on a non-skid surface (e.g., low pile carpeting) if available with the back of the chair against a wall for stability. There should be adequate room in front and on the sides of the chair for the examiner and participant to move freely.

Make sure the participant's feet are squarely on the floor in front of them. The participant should be seated in a position which allows them to place their feet on the floor with knees flexed slightly more than 90 degrees so that their heels are somewhat closer to the chair than the back of their knees. Feet should remain on the floor during testing. Stand in front of the participant (with arms extended, if appropriate) for the participant's safety when performing the chair stands.

Say to the participant "This is a test of strength and stability in your legs in which you stand up from a chair without using your arms. Fold your arms across your chest, like this, and stand when I say GO, keeping your arms in this position. Any questions? Ready, Go!"

If the participant's arms unfold, or they put one or both hands down on the chair to push up, or their feet come off the floor during testing, remind them to keep their arms folded snugly across their chest with feet on the floor and ask them to repeat the chair stand. It is OK for the participant to move a little forward in the chair before standing, but knees and hips should be flexed to approximately 90 degrees before standing. If the participant cannot rise without using arms, say "OK. Try to stand up using your arms to push off."

a. Scoring the SPPB Single Chair Stand

Score as follows: If the participant refuses to do the test or cannot understand the instructions, score "Participant refused."

If the procedure was not attempted because the participant was unable to perform the test, score "Not attempted/unable".

If the participant attempted but was unable to arise even using their arms, score as "Attempted, unable to stand."

If the participant uses arms to stand up, score as "Rises using arms."

If they stood up all the way without using arms, score as "Stands without using arms." Go on to Repeated Chair Stands. Skip repeated chair stand for all other responses.

14.4 ADMINISTRATION OF THE SPPB REPEATED CHAIR STANDS

Next the participant stands from a seated position five times as quickly as possible. Record the time it takes to stand five times. Say to the participant, "This time I want you to stand up five times as quickly as you can, keeping your arms folded across your chest." With the next instructions, cross your arms over your chest and then rise while emphasizing "full standing position," and sit while emphasizing "all the way down": "When you stand up, come to a full standing position each time, and when you sit down, sit all the way down each time. I will demonstrate two chair stands to show you how it is done." Count as you stand each time. Then begin the test. "When I say GO, stand five times in a row as quickly as you can without stopping. Stand up all the way and sit all the way down each time. Ready, Go!"

Start timing as soon as you say "Go." Count: "1, 2, 3, 4, 5" as the participant straightens to standing position each time. Stop timing when the participant stands the final time.

If the participant is unable to complete the chair stands correctly (e.g., is not coming to a full stand, lifts feet off the floor), stop the procedure, repeat the demonstration, wait 1 minute, and begin the procedure again. If the participant stops before completing five stands, confirm that they cannot continue by asking: "Can you continue?" If they say yes, continue timing for up to 1 minute. Otherwise, stop the stopwatch and record the number of chair stands that were completed. If 5 stands have not been completed by 1 minute, stop the test and record "Attempted, unable to complete 5 stands" as well as the number completed.

a. Scoring the SPPB Repeated Chair Stands

If the participant refuses to do the test or cannot understand the instructions, score "Participant refused." If the procedure was not attempted because the participant was unable to perform the test, score "Not attempted/unable." It is acceptable to question the participant to determine if the participant refused because they thought they would have difficulty, be unable to do, or it would be unsafe due to inability to perform well; these should be coded "Not attempted/unable".

If participant attempted but was unable to complete five stands without using their arms, score as "Attempted, unable to complete five stands" and record the number completed without using arms.

If five chair stands were completed, record the number of seconds, to a hundredth of a second, required to complete five stands.

14.5 ADMINISTRATION OF THE SPPB STANDING BALANCE

This is a series of timed, progressively more difficult, static balance tests. The level of difficulty increases as the lateral base of support decreases. The time (up to 10 seconds) that the participant can hold each position (i.e., side-by-side, semi-tandem, tandem) is recorded. Walking aids such as a cane or walker may not be used.

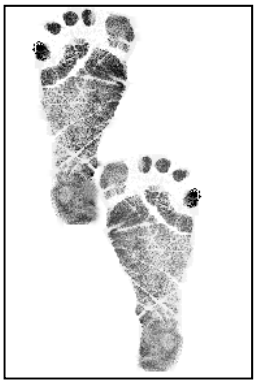
The standing balance test should be performed with the participant standing a little less than an arm's length from a wall to provide an additional source of support should loss of balance occur.

For each stand, describe the position to the participant and then demonstrate it while facing the participant. After demonstrating, approach the participant from the front and off to the side away from the wall. Offer your arm (the one away from the wall) for support while the participant gets in position.

If the participant feels it would be unsafe to try, probe for the reason, and reassure the participant that you will help them into the position and that they can use the wall for additional support. If they still feel they should not attempt it, record, "Participant refused" or "Not attempted, unable" (whichever is appropriate) for this and the more difficult stands and go on to the next test.

If the participant attempts the stand incorrectly, demonstrate it again. Time each stand. After 10 seconds for each stand, tell the participant to stop. If the participant loses balance before 10 seconds, record the number of seconds for which the stand was held. See figures for placement of feet for each type of stand.

To maximize time allotment for testing, the balance tests begin with the semi-tandem stand. If this position cannot be held for 10 seconds, the examiner should record results of the semi-tandem stand then describe and demonstrate the side-by-side stand, which is easier, and mark the tandem stand as "Not attempted/unable." If the semi-tandem position is held for ten seconds, the side-by-side position should be marked as "held for 10 seconds" and the tandem stand should be attempted.



a. Administration of the Semi-Tandem Stand

Begin by introducing the balance tests: "I'm going to ask you to stand in several different positions that test your balance. I'll demonstrate each position and then ask you to try to stand in each position for 10 seconds. I'll stand next to you to provide support if you lose your balance. Do you have any questions?"

Say, "First, I would like you to try to stand with the side of the heel of one foot touching the big toe of the other foot for 10 seconds. Please watch while I demonstrate. You may

put either foot in front. You can use your arms, bend your knees or move your body to maintain your balance. Try to hold your feet in position until I say stop. If you lose your balance, take a step like this. Hold onto my arm while you get in position." Allow the participant to hold onto your arm to get balanced. "When you are ready, let go." If you or the participant feels this stand may be too difficult, you may start with the side-by-side stand instead. (below).

Start timing when the participant lets go. Stop the stopwatch if the participant takes a step or grabs for support. Say, "STOP" after 10 seconds. Then go to the Tandem stand.

If the participant is unable to hold the semi-tandem stand for at least 10 seconds, do not attempt the tandem stand, but instead perform the side-by-side stand, which is less difficult, and then go to the walking tests.

b. Scoring the SPPB Semi-Tandem Balance

Based on the results from the semi-tandem stand, if you reason it would be unsafe for the participant to proceed to the more difficult tandem position, record "not attempted/unable" on the form for the tandem stand and continue to the walking tests. If the participant refuses or cannot understand the instructions, score "Participant refused." If the procedure was not attempted because the participant was unable to perform the test, score "Not attempted/unable." If the participant attempted the test but could not hold the position for at least 1 second, score as "Unable to attain position or hold for one second." If the participant held the position for at least 1 second but less than 10 seconds, score as "Holds position ≥1 but less than 10 seconds" and record the time to 0.01 second. If the participant held the semi-tandem stand for 10 seconds, score as "Holds for 10 seconds" and also score the side-by-side stand as "held for 10 seconds".

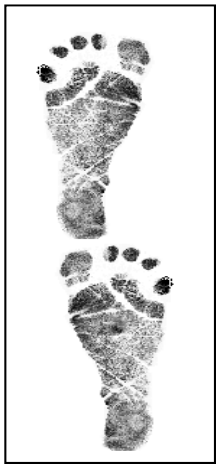
c. Side-by-Side Stand

"Now, I would like you to try to stand with your feet together, side-by-side, for 10 seconds. You can use your arms, bend your knees or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop. Hold on to my arm while you get in position." Allow the participant to hold onto your arm to get balanced. Say: "When you are ready, let go."

Start timing when the participant lets go. Stop the stopwatch if they take a step or grab for support. Record to 0.01 second the time the participant could hold this position. Say, "STOP" after 10 seconds.

d. Scoring the Side-by-Side Stand

If the participant refuses or cannot understand the instructions, score “Participant refused.” If the procedure was not attempted because the participant was unable to perform the test, score “Not attempted/unable.” If the participant attempted the test but could not hold the position for at least 1 second, score as “Unable to attain position or hold for one second.” If the participant held the position for at least 1 second but less than 10 seconds, score as “Holds position ≥1 but less than 10 seconds” and record the time to 0.01 second. If the participant held the position for 10 seconds, score as “Holds for 10 seconds”.



e. Administration of the Tandem Stand

The Tandem Stand is only administered if the participant is able to hold the Semi-Tandem stand for at least 10 seconds. “Now I would like you to try to stand with the heel of one foot in front of and touching the toes of the other foot for 10 seconds. Please watch while I demonstrate. You may put either foot in front. You can use your arms, bend your knees or move your body to maintain your balance. Try to hold your feet in position until I say stop. If you lose your balance, take a step like this. Hold onto my arm while you get in position. When you are ready, let go.”

Start timing when the participant lets go. Stop the stopwatch if they take a step or grab for support. Record to 0.01 second how long participant is able to hold this position. Say, “STOP” after 10 seconds.

If the participant holds the position for 10 seconds, go to the walking tests. If the participant attempts the Tandem Stand and is unable to attain the position or cannot hold it for at least one second, go to the walking test. If the participant held the position for at least 1 second but less than 10 seconds, perform a second trial of the Tandem Stand. Say “Now, let’s do the same thing one more time. Hold onto my arm while you get into position. When you are ready, let go.”

f. Scoring of the Tandem Stand

If the participant refuses or cannot understand the instructions, score “Participant refused.” If the procedure was not attempted because the participant was unable to perform the test, score “Not attempted/unable.” If the participant attempted the test but could not hold the position for at least 1 second, score as “Unable to attain position or hold for one second.” If the participant held the position for at least 1 second but less than 10 seconds, score as “Holds position ≥1 but less than 10 seconds” and record the time to 0.01 second. If the participant held the position for 10 seconds, score as “Holds for 10 seconds”.

14.6 ADMINISTRATION OF THE SPPB 4 METER USUAL WALK

Time to walk 4 meters at the participant’s usual pace is measured.

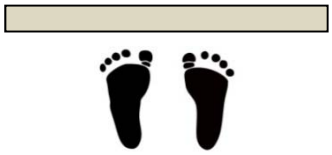
a. Walking course

If 4 meter space is not available, such as in a participant's home, a 3-meter course could be used with the distance marked on the data collection form.

The walking course must be free of obstacles and at least 5 meters long (4 meters plus at least an additional ½ meter on each end of the walking course.) See SPPB Overview for course layout. The course should be in an uncarpeted or low-pile carpeted, low traffic, and unobstructed corridor at least 122 cm (about 4 feet) wide. The start and finish lines will be marked by colored tape on the floor.

If necessary, participants may use walking aids, such as a walker or cane. Ask participants who arrive with walking aids if they think they can do this short walk without the device when showing them the course. Often, participants who have aids will feel very comfortable and are quite capable of walking the 4 meters without a walking aid when they see the length of the course. In these cases, the exam should be done without the aid.

Say to the participant: "I'm going to ask you to do a short walk over this 4 meter course two times. You will walk at your normal or usual pace for two trials. I will demonstrate. Place your feet with your toes behind, but just touching the starting line, like this."



"Walk a few steps past the finish line." Demonstrate by walking to the other end of the course at your usual pace, making certain you walk past the finish line before slowing or stopping."

b. Usual pace walk

Make sure the feet are in proper position. "Do you have any questions? When I say "Go", please walk at your normal pace. Remember to walk a few steps past the finish line." To start the test, say, "Ready, Go." Start timing with the participant's first movement.

Follow along a few paces behind and a little to the side of the participant so you can see when the foot crosses the finish line. Stop timing when the first foot fully crosses an imaginary plane extending vertically up from the ending line/tape. Record the time to the nearest 0.01 second.

Have the participant repeat the usual pace walk: "Let's try this one more time. Ready? Go."

14.7 GRIP STRENGTH

The grip strength assessment should be performed after the SPPB components and before the TMW, providing a rest period prior to the TMW. Grip strength is a commonly used measure of upper body skeletal muscle function, has been widely used as a general indicator of frailty and, in the absence of other measures of strength, is a good marker of global muscle strength. Grip strength is

often measured in the dominant hand or in both hands and the best result used in analyses. This assessment is modified slightly to accommodate time restrictions while maximizing physical function measurements; overall, it is focused on measuring maximal strength. Grip strength in the participant's preferred hand, usually the dominant hand, will be measured using an adjustable, hydraulic grip strength dynamometer. Allowing participants to choose the best side should be comparable to either testing one's dominant hand, as most will choose the dominant hand, or to choosing the best result of bilateral testing. Allowing participant preference will permit participants to choose non-dominant side if medical or other conditions, e.g. stroke, have impaired the dominant hand and testing that side would not necessarily represent global muscle mass or strength.

a. Exclusions

Grip strength exclusion is limited to those who have had surgery on both hands or both wrists in the previous 3 months. If only one side is affected, test the unaffected side. The test can be performed if the participant has a current flare-up of pain in their wrist or hand, for example arthritis or tendonitis. Be sure to record this information on the data collection form.

b. Equipment

Jamar Hydraulic Hand Dynamometer, which registers maximum kilograms of force during a trial, with adjustable handgrip.

Mouse pad for small rolled towel for wrist support

Table with adjustable height (moveable tray table preferred)

c. Equipment Calibration

Every six months: Check the calibration of the grip strength dynamometer by hanging 5 kg and 20 kg (or 10 and 50 lb) weights across the handle using two Velcro straps, one strap on each side of the dynamometer handle, or one wide strap that covers the whole handle. Lift the weights slowly from the floor while they are strapped to the dynamometer handle and record the maximum kilograms registered. The lifting motion should be very slow and smooth, and the weight should remain evenly distributed between the two sides of the handle. Repeat the procedure three times and record each result.

Average the three calibration trials. The dynamometer should be accurate within ± 2 kgs for the average of the three calibration trials. It may be necessary to send the dynamometer to the manufacturer for repair and recalibration. **DO NOT attempt to recalibrate the dynamometer yourself.** Calibration problems can be caused by dropping the dynamometer or by leaks in the hydraulic system.

d. Administration of the Grip Strength

The participant should be seated at a standard height table or on a seat with a moveable tray table attached.

"The next test I'll ask you to do is the grip strength test. This device is used to measure the strength in your hand. Even when you squeeze the grip bars as hard as you can, the bars will not feel like they are moving much at all. Before starting, I will ask you a few questions to make sure it is safe for you to do this test."

Determine if the participant has an acute or recent flare of arthritis in the hand that will be tested. Ask, "Do you have any pain or arthritis in either hand or wrist?" if participant answers "Yes", ask, "In which hand or wrist is the pain or arthritis?" Record response. Next ask, "Has the pain or arthritis in your hand(s) or wrist(s) gotten worse recently?" Record response. "Will the pain or arthritis in your hand(s) or wrist(s) keep you from squeezing as hard as you can?" Record response. Pain or arthritis that has gotten worse recently is not an exclusion for this test.

"Have you had any surgery on your hands or wrists in the past three months?" Record response. If the participant says "No", proceed with test; if they answer "Yes," ask them which hand or wrist was operated on, record response, and do not test that hand.

The examination is done with the participant seated facing a table at shoulder level with arm to be tested extended in front of participant approximately 90° and resting on the table with the elbow held straight (180°). The dynamometer is held perpendicular to the table in the hand to be tested, just off the table edge. The wrist should be resting on a mouse pad or rolled towel if mouse pad is not available. Correct grip and participant positions are shown below. Demonstrate the correct grip and arm position while seated at the table, if necessary.

Figure 1. Grip position

Figure 2. Arm Position

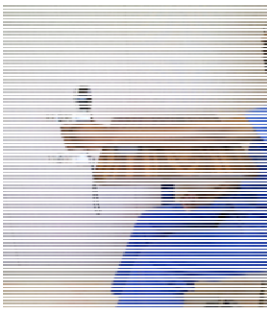


Figure 3. Arm Position

Figure 4. Mouse pad for wrist support

Ask "Which hand is your preferred or best hand to test for maximum strength?" This response determines which hand is tested unless this side was excluded in the previous screening questions. Record response on form. "Please extend that arm in front of your body and rest it on the table with your arm straight and wrist on the mouse pad. Grip the two bars in your hand like this and squeeze gently to get the feel of it." Demonstrate proper positioning of the dynamometer then place wrist strap around the participant's wrist and position participant. Adjust the grip size until the participant is holding the dynamometer comfortably (this will almost always be the second setting). If the handle hits the participant's hand distal to the second knuckle the grip size should be smaller. If the

participant's natural finger nails are hitting their palm the grip size needs to be larger. "Are the bars the right distance apart for a comfortable grip?" Readjust as needed prior to starting the test until a comfortable position is attained. Allow one submaximal practice trial to determine if the participant understands the procedure and that the grip size is appropriate.

When ready for the practice trial, say, "Now try it once just to get the feel of it. For this practice, just squeeze gently. It won't feel like the bars are moving, but your strength will be recorded." Show dial to participant after squeezing then reset to zero. "You'll do this two times. When I say "squeeze", squeeze as hard as you can. Ready? Squeeze! Squeeze! Squeeze! Now, stop."

Perform two trials with 15 to 20 sec rest in between. After the first trial, reset the dial to zero, and say "Now, one more time. Squeeze as hard as you can. Ready. Squeeze! Squeeze! Squeeze! Now, stop." Set the dynamometer to zero prior to each attempt. Record the kilograms from the dial to the nearest 2 kilograms onto the form. If the reading is exactly between two readings on the scale, round up to the next higher even number. Reset the dial to "0" after each trial.

e. Scoring of the Grip Test

Score as follows: if the participant refuses or cannot understand the instructions, score "Participant refused." If the participant was unable to perform the test, score "Unable to do." If the participant was excluded due to recent surgery, record "Excluded". If the participant completed only 1 trial, record "Did 1 trial"; if he/she completed both trials, record "Did 2 trials". Round to nearest kg; if exactly between two readings on dynamometer, round to the nearest whole number between the even numbers shown. For example, if the reading is midway between 26 and 28, record 27. Round readings that are less than half way between two even numbers down; round readings that are more than half way round up. Reset the dial to "0" after each trial.

14.8 ADMINISTRATION OF THE UNINTENTIONAL WEIGHT LOSS QUESTIONS

The goal of these question is to document unintentional weight loss that has not been regained. In the first question, the participant is asked if s/he has lost 10 pounds in the past year. If the participant has not lost more than 10 pounds, record "No" and skip to question 4. If the participant reports s/he has lost about 10 or more pounds, the response should be coded as "Yes" and the interviewer should then ask "About how much lower is your weight now than a year ago?" This will provide an estimate of weight loss in whole numbers of ten or greater. Record response. The last question simply asks if the participant was trying to lose weight.

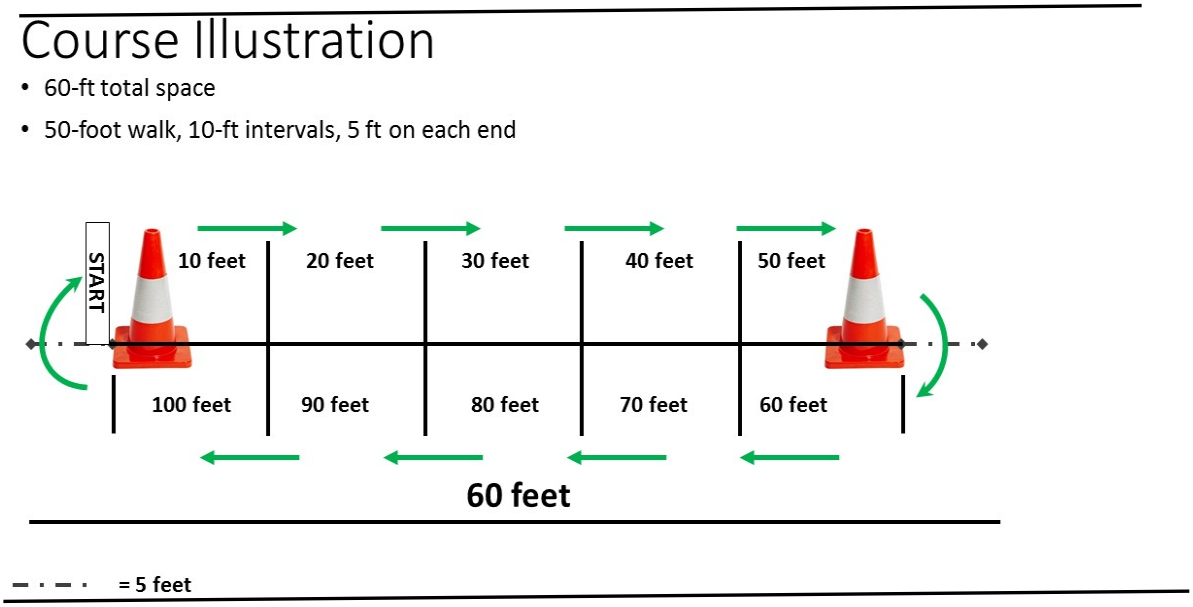
14.9 ADMINISTRATION OF THE TMW

a. Footwear

To reduce the effect of different footwear on test performance, the TMW should be performed in tennis shoes or comfortable walking shoes with minimal or no heels. The participant should be instructed during the pre-visit instructions to wear or bring comfortable walking shoes to the clinic.

b. Course Set-up

For consistency, the walking course length will be 50 feet with an additional 5 feet on each end, laid out in an unobstructed, dedicated corridor. Use traffic cones to indicate the beginning and end of the course. The cones should lie fully within the 50 foot course (see figure). Participants will walk in a clockwise direction. Place a 1.5 foot length of tape across the floor to the left of one of the cones to mark the start of the course.



For easy access, the examiner should wear the stopwatch around his/her neck. To use the Ultrak 410 stopwatch (pictured at right), first press the reset button at the top left so the display shows **000 00”00**. To begin timing, depress the top of the right-hand button labeled START/STOP watch and press again at the bottom right to stop. The total time will appear on the primary display as minutes’seconds”hundredths of a second.

14.10 SAFETY ISSUES AND EXCLUSIONS

If there is an unclear answer to an exclusion question the final decision to test rests with the medical supervisor. Any one of the following is cause for exclusion from the TMW and must be documented on the data collection form:

- Participants unable to complete the 4-meter walk without a walking aid
- Resting heart rate >120 bpm

- Systolic blood pressure ≥190 or diastolic >110
- Cast or immobilizing device on leg

Blood pressure: Consult blood pressure data collected earlier in the clinic visit.

Requires walking aid: Some participants who complete the short walks without a walking aid may be uncomfortable and/or unwilling to attempt a longer walk, such as the TMW, without the walking aid. Use of a walking aid is not allowed in the TMW.

For most participants, full administration of the TMW should take no longer than 4-5 minutes.

14.11 ASSESSMENT OF TEST ELIGIBILITY AND EXCLUSION CRITERIA.

1) Review exclusion criteria above and record responses on data collection form. Before beginning the TMW, tear off a piece of tape that will be used to mark the participant's stopping point on the course.

2) Provide a brief, general description of the TMW to participants who have no exclusion criteria. Examiner should have participant sit in a chair near the beginning of the walking course.

Script: "This is an activity that shows how physically fit you are by seeing how far you can walk in 2 minutes. I will ask you to walk as fast as you can until I ask you to stop. I know this is hard for some people so don't worry if you have to slow down or rest. If you do stop or slow down, start walking again as soon as you feel you are ready to do so. Is there any reason you cannot do the walk? ***[*wait for response*]*** Does anything hurt or are you in pain?***" [*wait for response*]***

If participant does not feel he or she can do this task, note this on the record sheet and continue with another measure.

Script: "You and I will not talk while you are walking because this might make you walk more slowly. I will, however, let you know how much time you have to walk and when you are almost done.**"**

While demonstrating first part of the task, say:

Script: "You will start with your feet behind this line. When I say 'Go,' you will walk back and forth around the cones as fast as you can without running or hurting yourself. You will begin after I say 'Ready, 3, 2, 1, Go!' As you pass the cone, do not stop or slow down. When I tell you to stop, stop where you are on the path until I come to you. If you stop before I say "Stop," I still need you to remain at that point if you are able.**"**

Demonstrate task and say:

Script: "Watch me as I show you what you are going to do. You see that I am walking fast but not running and that I am not slowing or stopping when I pass the cone. When I say "stop", stop in place like this.**"** (Stop where you are and stand still on the path.) **"**Do you have any questions?**" "**Answer questions as necessary.

FIGURE 1. Stopwatch at 0:00:00 seconds

Script: Stand with your toes at the starting line. Ready, 3, 2, 1, Go!**"**

Start timing the participant when the first foot crosses the start line, before making first footfall. Examiner should begin marking off the number of cones on the data form as they are completed; all turns around the cone away from the start line should be odd numbers and all turns around the cone nearest the start line should be even numbers. The examiner should walk with the participant, slightly behind and just to the side of the participant.

The examiner should provide the following feedback: After 1 minute* say:

Script: "You are doing well. You have 1 minute to go."

*If participant is resting at one-minute reminder, encourage him/her to continue and change statement to:

Script: "You have only 1 minute left. Rest as long as you need; start walking again as soon as you feel able to do so."

When time reads 1:45, tell the participant:

Script: In a moment, I'm going to ask you to stop. When I do, just stop right where you are and I will come to you.

When five seconds remain, examiner should count down:

Script: "5, 4, 3, 2, 1, stop."

Stop the stopwatch and put a piece of tape on the floor behind the participant's heel that is on the floor at the end of the two minutes. Measure distance from the last cone passed to the edge of the tape that touched the participant's heel. Record the distance in feet on the data form. If the distance is 6 inches or more inches or more beyond a foot marker, round up. Otherwise, round down. If the participant stopped for a rest, mark this on the data collection form.

a. Scoring Process

The participant's raw score is the distance walked in two minutes, reported in feet or meters (and fractions thereof). This score can be used as a raw measure or converted to the Toolbox normative scale scores.

b. Interpretation

Cardiorespiratory and muscle endurance are important components of physical fitness and contribute to both performance and health status. Greater distance walked in the TMW is suggestive of better endurance. Normative scale scores are provided in the NIH Toolbox: (http://www.nihtoolbox.org/WhatAndWhy/Motor/Endurance/Pages/default.aspx).

For the endurance component of the NIH Toolbox Motor assessment, the fully adjusted scale score can be used in the interpretation of normative scores, because it takes into account gender, age, ethnicity and education differences. Thus, it provides a level playing field for evaluating participants' performance since differences in performance may exist as a function of some of these demographic variables (most notably, gender and age). When interpreting endurance normative scale scores, higher performance is indicative of better endurance. A fully adjusted scale score that is 2 SDs below the mean (scale score of 70 or below) is suggestive of motor dysfunction; further evaluation by a physician or physical therapist may be warranted. People with better endurance are able to complete daily tasks and are more physically fit to pursue leisure activities and accomplish higher-intensity workloads. The clinical significance of endurance, as measured by timed walk tests, to morbidity and mortality outcomes has been reported in healthy and clinical populations across the age span.

c. Symptoms during/after the TMW

Participants could experience symptoms during the walk. Mild symptoms could include feeling tired or flushed, dizziness, muscle soreness, cramping, or have other muscle or joint irritation. If mild symptoms occur, tell the participant to slow down. If chest pain/pressure/tightness occurs, quickly approach the participant, mark the stopping distance and record the time and distance. Assist the participant to a chair, or if necessary take a chair to the participant. If the participant confirms chest pain or pressure/tightness after resting for 5 minutes notify the nursing or medical staff on site. Symptoms of chest pain, tightness, or pressure with walking that do not resolve with rest are considered a medical emergency. Even if the symptoms resolve with rest this should be reported to the participant and with the participant's authorization to the physician of record as an alert. If the reason for stopping is chest pain, tightness, or pressure, discontinue the test and do not resume.

Except for chest pain/pressure/tightness, the test should not be stopped cold. Participants may resume walking from the marked stopping location if symptoms such as flushing, shortness of breath, cramping, or fatigue resolve and they are willing. Participants can resume walking at the

faster pace or continue with the slower pace during the remainder of the walk after a rest period. . Always record the reason for stopping the walk on the data collection form.

d. Training and Certification for SPPB

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

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

Certification will include:

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

The following elements must be demonstrated successfully for certification:

Chair stands

☐ Back of chair against a wall
☐ Script correctly and clearly delivered
☐ Correctly demonstrates two stands, emphasizing full stand and return to complete sit
☐ Says "Ready? Go" for each test
☐ Records timed measure within 0.5seconds of QC officer or designated personnel
☐ Counts each chair stand and records stand if less than 5
☐ Records and explains unusual values
☐ Starts timing with "Go", stops with final stand or one minute
☐ If task was not performed, codes and explains reasons

Standing balance

Side-by-side stand

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

Semi-tandem stand

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

Tandem stand

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

4-meter walk

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

14.12 QUALITY CONTROL

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

14.13 TRAINING AND CERTIFICATION FOR GRIP STRENGTH ASSESSMENT

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

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

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

Certification will include:

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

QC elements required for certification are:

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

14.14 TRAINING AND CERTIFICATION FOR THE TMW

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

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

- Read and study the manual
- Questions regarding unintentional weight loss questions will be addressed during central training and certification for the TMW will include administering these questions.
- Attend ARIC training session on performance test administration techniques (or observe administration by experienced examiner)
- Practice on other staff or volunteers
- Discuss problems and questions with local expert or QC officer
- QC officer or designated person may review video of 2 performances if necessary

Certification will include:

- Complete training requirements
- Recite exclusions
- Conduct exam on two volunteers:
- According to protocol, as demonstrated by completed QC checklist
- Distances recorded are within $\pm$ 2 1 foot of QC officer measurement

14.15 QUALITY ASSURANCE/CERTIFICATION CHECKLIST

Preparation

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

2-Minute Walk

- Instructs participant to walk as quickly as they can
- Encourages participant every lap
- Gives 1 minute warning
- Marks and records number of cones passed

- Offers rest period if needed and encourages resting participant to resume when ready
- Gives participant notice when 1:45 time elapsed and walks to participant at 2 minutes
- Places tape behind participant's heel
- Records whether or not the participant completed the walk and if not, why
- Reviews form for completeness
- Accurately measures and records distance
- Describes appropriate responses to symptomatic participants during TMW

1. Bohannon RW, Wang Y-C, Gershon RC. Two-Minute Walk Test Performance by Adults 18 to 85 Years: Normative Values, Reliability, and Responsiveness. *Archives of physical medicine and rehabilitation.* 2015;96(3):472-477.
2. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2001;56(3):M146-156.

15. PERIPHERAL NEUROPATHY ASSESSMENT – MONOFILAMENT TESTING

15.1 OVERVIEW

Peripheral neuropathy is characterized by numbness, reduction or loss of temperature and pain sensation, tingling, and muscle weakness and atrophy in the lower extremity. Peripheral neuropathy is a common complication of diabetes. Reduced sensation can lead to a number of complications such as foot ulcers, undetected minor trauma—which can lead to more major complications, and even amputation.

Monofilament testing is a simple, noninvasive test to identify people who have lost protective sensation. The test uses a nylon monofilament to evaluate touch-pressure sensation in the feet. It is commonly used in the clinic as a screening test for peripheral neuropathy.

The policy of ARIC is to report all clinically relevant tests back to participants. Since monofilament testing to detect peripheral neuropathy is a clinically relevant test, the results will be reported to participants (or their doctor with permission). Reports will indicate whether the participant has at least one insensate site on either foot and whether lesions or ulcers are found in a visual inspection of the feet. Standard ARIC procedures will be used to report the test results back to participants. There are no “alert values” from this test that require expedited notification.

15.2 BACKGROUND

While monofilament testing is commonly recommended as part of a foot exam for persons with diabetes, standard protocols with established sensitivity and specificity are lacking. A recent systematic review found only three studies had validated monofilament testing with a gold standard of nerve conduction tests, and these three studies used different sites of the foot and different numbers of tests per site, precluding a formal meta-analysis of the sensitivity and specificity of monofilament testing (Dros 2009). Numerous organizations have recommended monofilament testing at four sites per foot, and these are the four sites tested in ARIC (National Diabetes Education Program; American Diabetes Association).

The protocol used here is modeled after the protocols from the National Health and Nutrition Examination (NHANES) for peripheral neuropathy (monofilament) testing, but with two important differences. First, NHANES only tests three sites per foot, the hallux, the first metatarsal head, and the fifth metatarsal head. Here, we have added an additional site, the third metatarsal head, because several studies have shown that the third metatarsal head is highly sensitive (Lee 2003, Mayfield 2000). Second, NHANES tests each site between one and three times, depending on how the participant answers the first test at each site. If the participant answers correctly on the first test, then the test is not repeated. The test is repeated until two of three answers are the same. Presumably this is a timesaving effort. Here, we have chosen to test each site three times in all participants, both to reduce misclassification and also reduce the complexity of administrating the

monofilament test. Additionally, while we have proposed one method to “score” the monofilament test to determine if peripheral neuropathy is present, other definitions are possible, and using a standard number of tests per site makes it easier to develop alternative scoring algorithms. This protocol allows for comparison with NHANES because the protocol for NHANES is “nested” within our protocol, and thus one can calculate the number of people who have peripheral neuropathy by either NHANES definition or by the ARIC definition.

In NHANES, a site is considered insensate if the person incorrectly identifies the monofilament for two of three tests, and a person is considered to have peripheral neuropathy if at least one of six sites (three sites per foot) is insensate. Gregg et al. (2004) reported a sensitivity of ~85% and specificity of ~80% for the NHANES protocol, but some of the studies the authors of this report cite included studies of persons with foot ulcers and used a "gold standard" of vibration testing, which is not an ideal measure. In contrast, Lee et al. (2003) conducted one test for each of 10 sites on one foot, and found that using a definition of peripheral neuropathy as unable to correctly sense the monofilament at either the 3rd or 5th metatarsal head yielded the best sensitivity (93%) and specificity (100%), but their sample size was only 37 (29 of whom had peripheral neuropathy according to a nerve conduction test). The classification of insensate and of peripheral neuropathy used in ARIC are described below. Based on the literature we submit that our definition should be more sensitive than the NHANES definition because an additional site is included, but might have slightly lower specificity than NHANES.

15.3 PROCEDURES

a. Preliminary Evaluation

Before conducting the monofilament testing the foot should be examined for amputations, lesions, and calluses. These abnormalities are described below. Do not remove bandages or compression stockings. If bandages or stockings prevent observation of the feet, enter ‘could not obtain’ and select the appropriate comment.

Examine the plantar surface of the foot with your hands for the presence of calluses when assessing the foot for abnormalities. Calluses are not always visible to the eye and it is important to confirm that the site to be tested for peripheral neuropathy is free of calluses. Although calluses are not recorded as a data point for ARIC, the presence of very large and thick calluses may interfere with peripheral neuropathy testing. If a callus is present, the technician should lightly touch the plantar surface of the foot in the metatarsal area to determine the thickness and spread of the callus. If the callus covers the entire metatarsal area, or the entire top half of the foot, monofilament testing cannot be done on that site. The technician will note the callus by marking ‘could not obtain’ with ‘callus’ as the reason for that site.

Observe both feet for amputation and lesions as described below.

b. Amputation

Record as 0 (no amputation), or 1-10 as shown in figure below.

0. None

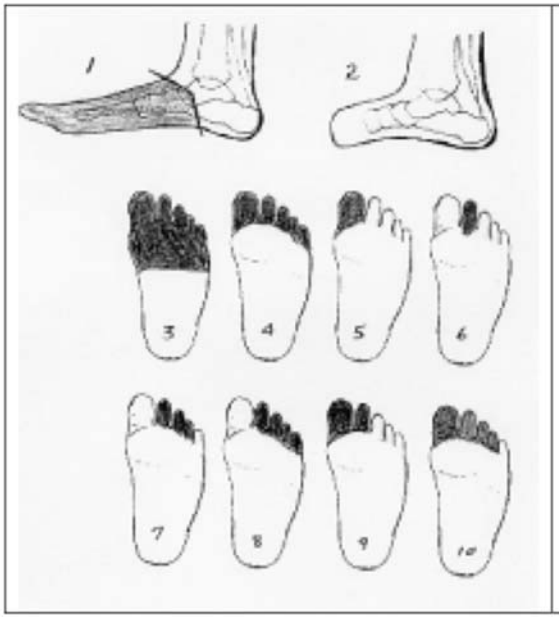
1. Entire Foot- Amputation at the ankle or above. This includes any amputation that is higher than a transmetatarsal or partial foot amputation

2-4. Partial Foot- (Transmetatarsal) Amputation of the great toe and all of the other toes

5. Great Toe- Amputation of great toe only

6-8. Other Toe(s)- Amputation of one to four of the other toes. Does not include the great toe.

9-10. Great Toe and Other Toe(s)- Amputation of the great toes and one to three of the other toes. If all four of the other toes are missing, this would be defined as a partial foot.

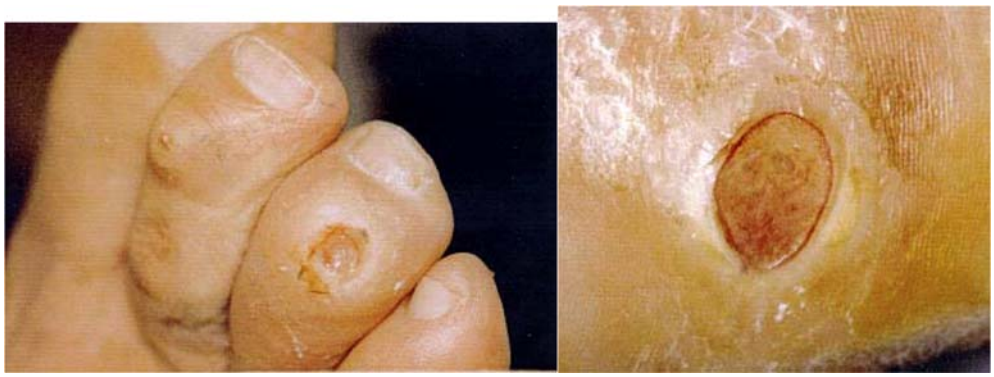


1. Entire foot
2. Partial foot
3. Partial foot
4. Partial foot
5. Great toe
6. Other toe(s)
7. Other toe(s)
8. Other toe(s)
9. Great toe and other toe(s)
10. Great toe and other toe(s)

(From NHANES Lower Extremity Disease Procedures Manual)

c. Lesions

Lesions may develop at pressure points on the feet especially when pain sensation is diminished or absent (as in neurotrophic ulcers in people with diabetic neuropathy). For this study, lesions are defined as bandages, blisters, ulcers, abrasions, lacerations, and sutures. Fissures between the toes will not be defined as lesions. Bandages or pressure stockings covering all or part of the foot will not be removed for this assessment even if the study participant volunteers to remove them. The same is true for elastic or pressure stockings. The pictures below are examples of types of lesions that may be seen of the foot.



(From NHANES Lower Extremity Disease Procedures Manual)

For each foot, note if there are any lesions present, and record as any lesions on both feet, right foot only, left foot only, or none.

15.4 EXPLAINING THE MONOFILAMENT TESTING

The procedures for monofilament testing must be explained and demonstrated to the participant. If it becomes clear that the participant cannot follow the instructions for any reason, the monofilament testing should be skipped. The script and demonstration are read and performed by the technician as shown on the form and explained in the explained in the question-by-question instructions.

15.5 SITES TO BE TESTED

Both feet will be tested at four locations (shown in red below in the diagram below):

Plantar – hallux

Plantar –first metatarsal head

Plantar—third metatarsal head

Plantar—fifth metatarsal head

The order of the testing sites will be randomly determined to allow for better discrimination of sensation by the participant. The random assignment will be generated once and all participants will receive the testing in the same random order (see Table below for randomly generated order). The participant should not be able to see which part of the foot is being tested.

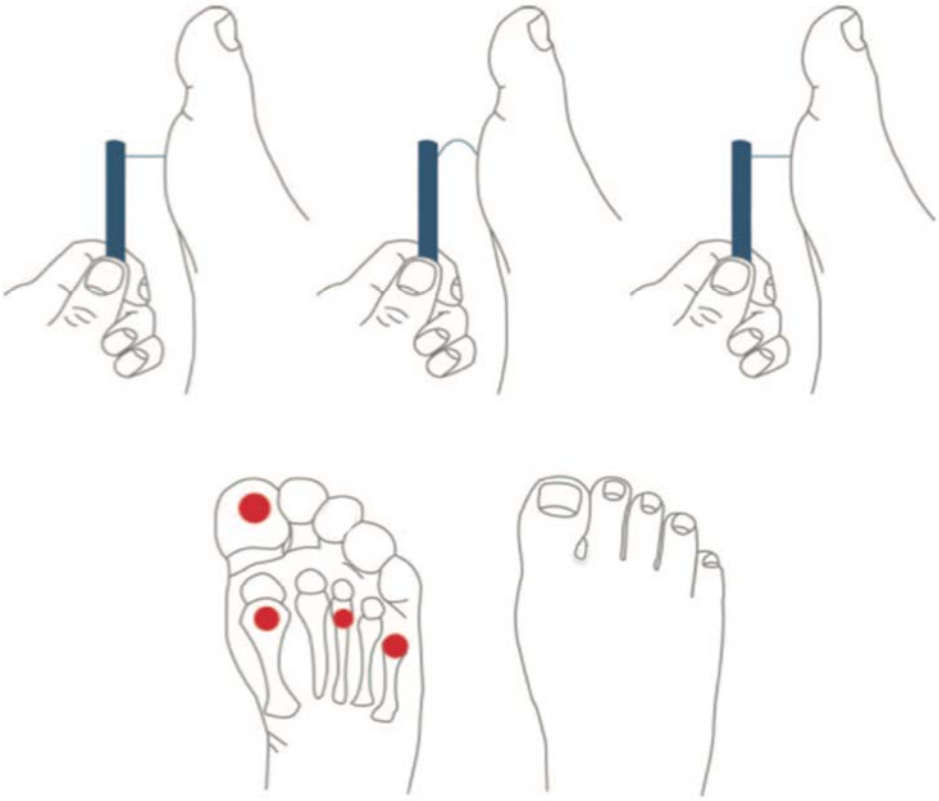


Figure 2—Upper panel: *For performance of the 10-g monofilament test, the device is placed perpendicular to the skin, with pressure applied until the monofilament buckles. It should be held in place for ~1 s and then released.* Lower panel: *The monofilament test should be performed at the highlighted sites while the patient's eyes are closed.*

From Bolton et al. Diabetes Care 2008 (with minor edits).

15.6 STANDARD PROCEDURES

- The participant will be in the supine position, resting quietly.
- The examiner should wear latex gloves.
- Use the 0.5/10 gram filament to test sensation.
- Starting with the left foot, follow the order in the table (below)
- Check the table for the interval (A or B) in which to apply the stimulus.
- Ask the participant to close his/her eyes.
- Test the first site:
    - When applying the filament, say out loud "A, B."
    - Do not change the inflection in your voice with the interval change.
    - Apply the filament to the skin's surface at either Interval A or Interval B as determined randomly by the computer as per above.
    - Apply the filament perpendicular to the skin's surface.
    - The approach, skin contact, and departure of the filament should be approximately 1.5 seconds duration.
    - The participant can choose one of three options:
        - Interval A
        - Interval B

        - Unable to determine the interval in which the stimulus was applied (participant could say: “I don’t know”, “I’m not sure”, or “Could you repeat the test” or a similar comment)
    - Record the response as one of the following options:
        - A
        - B
        - Unable to determine (U)
        - Could not obtain (O)
            - Callus/Scar/Necrotic Tissue/Bandage/Amputation (O)
            - Technician error (T)
- Each site will be tested three (3) times.
- If there is a callus, scar, or necrotic tissue at a site, do not perform the test and record “Could not obtain” for all tests at that site.
- Repeat on the right foot.
- After the exam is completed, clean the monofilament and replace in the case.

15.7 DEFINITION OF RESPONSES

- A: participant chose interval A
- B: participant chose interval B
- Unable to determine: when the participant is unable to determine whether the stimulus was applied in interval A or B.
- Could not obtain:
    - O: when the site to be tested cannot be tested for whatever reason (amputation, callus, bandage, cast, etc.),
    - T: if there was technician error in applying the stimulus. Possible technician errors:
        - The technician misstated A or B to the participant
        - The filament was applied on the wrong interval.
        - The filament was applied on both intervals.
        - The filament was not applied with the standard amount of force.
        - The filament was not placed on the site being tested.

15.8 DETERMINATION OF PERIPHERAL NEUROPATHY

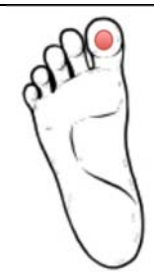
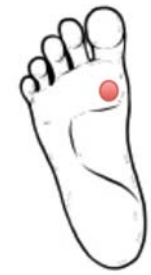
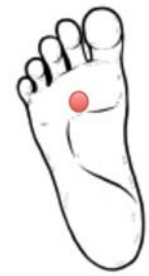
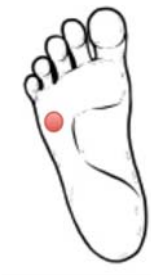
- For each site, if ≥2 responses are correct (participant chooses the correct interval A or B in which the monofilament was applied), then the site is sensate. If ≥2 responses are either incorrect (participant chooses the wrong interval A or B) or Unable to Determine, then the site is insensate.
- For each foot, if 0/4 sites are insensate, then the foot is normal. If ≥1/4 sites are insensate, then there is peripheral neuropathy.

15.9 DATA COLLECTION ELEMENTS

1. Amputations, right foot (enter value from 0 to 10, as defined above)
2. Amputations, left foot (enter value from 0 to 10, as defined above)
3. Lesions (None, right foot, left foot, both feet)
4 – 28. Results of monofilament testing, from table below.

15.10 ORDER OF TEST SITES AND ASSIGNED INTERVALS TO APPLY THE MONOFILAMENT

Foot	Site	Location	Apply During Interval A or B	Response (A, B, U, O, T)*
LEFT	Third Metatarsal Head		Test 1: A	
			Test 2: A	
			Test 3: B	
LEFT	Fifth Metatarsal Head		Test 1: A	
			Test 2: B	
			Test 3: B	
LEFT	First Metatarsal Head		Test 1: B	
			Test 2: A	
			Test 3: B	
LEFT	Hallux		Test 1: B	
			Test 2: A	
			Test 3: A	
RIGHT	Hallux		Test 1: A	

			Test 2: B	
			Test 3: A	
RIGHT	First Metatarsal Head		Test 1: A	
			Test 2: B	
			Test 3: B	
RIGHT	Third Metatarsal Head		Test 1: B	
			Test 2: B	
			Test 3: B	
RIGHT	Fifth Metatarsal Head		Test 1: A	
			Test 2: B	
			Test 3: A	

*Response definitions: A: Participant chose A; B: participant chose B; U: Participant unable to determine; O: callus, scar, necrotic tissue, amputation, bandage, or other; T: Technician error

15.11 REPORTING THE TEST RESULTS TO PARTICIPANTS

General statement: This examination tests your ability to feel a filament pressed on the bottom of your feet. We tested four places on each foot. *Part A:* This examination showed that you have <normal, decreased> sensation <in your right foot, both feet> *Part B:* and <normal, decreased> sensation in your left foot. *Part C:* We were not able to collect enough information to report results <on your right foot, on your left foot>.

- If a foot is amputated, the statement for that foot will be suppressed.

- Statement about lesions (only reported if lesions found): We found lesions on <both feet/your right foot/your left foot> that may warrant follow-up with your clinical provider.

15.12 QUALITY ASSURANCE

Study technicians are certified following central training. Indicators of data completeness and quality are computed periodically by the Quality Control Committee and distributed for review by the study leadership. Since the monofilaments used in peripheral neuropathy assessments eventually become worn, bending occurs with less pressure over time. To maintain the proper 10 g buckling force the monofilaments are replaced after use on approximately 50 participants, as specified in Manual 12. Replacement of the monofilament is monitored with the use of a log (Manual 12).

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16. ADDITIONAL ANCILLARY STUDIES

16.1 ZIOPATCH

ARIC cohort members participating in Visit 6 are invited to wear a Zio XT Patch monitor for two weeks and keep a symptom diary, to assess the occurrence of subclinical atrial fibrillation (AF). Participants are instructed to activate a trigger on the monitor should they experience a symptom of arrhythmia (such as palpitations, irregular heart beat sensation, “skipped beat” sensation, chest discomfort, dizziness, and fainting), and to document the symptoms in a symptom diary. Three days after application ARIC staff calls the participant to answer any questions; on day 10 following application ARIC staff calls the participant to remind them to mail the Zio XT Patch monitor and symptom diary to iRhythm. If application of the monitor at the field center or during an ARIC home examination is not possible, participants have the option of self-application of a monitor mailed to them, after return of a signed informed consent. A history of allergic skin reactions to adhesive tape, or the inability to mail the device back to iRhythm preclude participation in this study.

A standard report of study results is prepared centrally by iRhythm and is downloaded daily by the EPICARE Center at Wake Forest University. EPICARE personnel review the main arrhythmia diagnoses and ECG tracings on an ongoing basis, prior to transferring the results to the ARIC Coordinating Center where results are made available to the field centers to be shared with the study participants and their providers of medical care.

This study is conducted as ancillary to ARIC-NCS (PI: Lin Y. Chen, MD), and fully integrated into the Visit 6 examination. The study protocol and its associated materials are described in ARIC Visit 6 Manual 21: ARIC Visit 6 Atrial Fibrillation (https://www2.cscc.unc.edu/aric/aric-ncs-manuals).

16.2 ABI AND PULSEWAVE VELOCITY

Pulse wave velocity (PWV) and the ankle-brachial ratio of systolic pressure (ABI) are measured in ARIC-NCS Visit 6 as part of an ancillary study supported by the National Institute on Aging, NIH. PWV and ABI are measured simultaneously on participants resting in the supine position using an OMRON VP-1000 plus device. The measurement protocol and instrumentation (see Manual 24) are standardized to those used during the Visit 5 examination. All ARIC cohort members who take part in Visit 6 are invited to have PWV and ABI measurements.

17. DATA INVENTORY

A data inventory is done after all interviews and examination procedures have been completed and prior to the Exit Interview. At the field center's discretion, this can be done while the study participant changes into street clothes. 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, and adverse event form is filed.

To meet its obligations to participants, the study notifies participants or their caregivers about a poor performance on their cognitive status assessment (failure on two cognitive domains is notifiable). This information is sensitive, and is presented to the study participant – or the proxy/caregiver if present – during the exit interview to avoid a notification by letter. Notification of cognitive deficits recorded in the medical record could adversely affect a participant's ability to obtain long term care insurance in the future. A letter summarizing this information (see Manual 17) is therefore handed to the participant / caregiver, with a verbal explanation that does not deviate from the contents of the

letter. If under exceptional circumstances this letter must be mailed, it is addressed (only) to the study participant or the proxy.

If the participant is not eligible for Stage II s/he is thanked for participating in the ARIC exam visit and asked whether he/she has any remaining questions or any concerns.

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 Participant Safety Screening Form (PSA), 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 the DMS, 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 and the measurement of bioimpedence. 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 Participant Safety Screening form (PSA) 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 6 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 bioimpedence 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 Safety Screening 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 6 Exam Checklist. Any discrepancies between exclusion conditions recorded on the PSE/PSS 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. 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. The possibility of hypoglycemia with a 12-hour fast is diminished by routine inquiry during the scheduling of the examination visit about reasons which should exempt the participant from fasting. 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 below), 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 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 UPS IN ARIC

OHRP considers unanticipated problems to include any incident, experience, or outcome that meets <u>all</u> of the following criteria:

a. Unexpected;
b. Related or possibly related to participation in the research; and
c. 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 ARIC DMS (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 Coordinating Center 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 Coordinating Center for the NHLBI, the OSMB, and the Steering Committee. The reporting schedule of AEs and UPs in ARIC is presented in Table 19.1 (below).

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 Averse 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	48 hrs.	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.
Time / Schedule	Immediate	N.A.	N.A.	N.A.	N.A.	N.A.

19.11 EXCLUSIONS FROM STUDY PROCEDURES

a. Exclusion from Any Study Component

SBP >=200 or DBP >120 (Stop exam visit, arrange for urgent care; if technician unaware, this alert condition is triggered on entry into DES)

b. Exclusion from Bioimpedence 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 120 bpm or greater; the participant has a systolic blood pressure >190 mmHg; or the participant has a cast or other immobilizing device on a leg

19.12 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 change back into their street clothes and participate in the exit review and reschedule the clinic exam on another day.

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 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 Coordinating Center, 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 Coordinating Center 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 7) 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 Coordinating Center 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 id 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). Sample copies of the summary of study results are included in Appendix 6.

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 Report and Referral 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 Coordinating Center. The timeliness of this process and its successful completion according to study protocol are included in the quality analyses performed by the Coordinating Center and are periodically reviewed by the Quality Control Committee.

20.4 ACTIONABLE STUDY RESULTS

a. Seated Blood Pressure

Three measurements of seated blood pressure are recorded with a 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 2014 Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8) *JAMA* 2014;311(5):507-520. See 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 20.1 provides an overview of conditions and values reported to the ARIC study participants according to threshold values and the accompanying scripts.

Table 20.1. Classification of Blood Pressure in Adults Aged 18 Years or Older, and Recommended Action per JNC 8*

Age Group	Blood Pressure Goal -- Ppt. does not have Diabetes or CKD	Blood Pressure Goal -- Ppt. has Diabetes and/or CKD
Age <60 years	SBP <140 and DBP <90 mm Hg	SBP <140 and DBP <90 mm Hg
Age ≥60 years	SBP <150 and DBP <90 mm Hg	SBP <140 and DBP <90 mm Hg

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

* Source: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8) JAMA. 2014;311(5):507-520.

** Diagnosis of hypertension must be based on two or more readings taken at each of two or more visits following an initial screening.

1.

JNC 8 states that blood pressure classifications and referral recommendations are based on the average of two or more readings 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. In deciding whether a participant meets criteria for an alert level, the average of the 3 readings displayed by the Omron device is used. The data form include fields for these averaged values and for any actions taken.

When recommendation for follow-up of DBP and SBP are different, the shorter recommended time for recheck and referral is given precedence for participants not taking antihypertensive drugs. Unless an immediate referral (Diastolic BP $\geq$120 mmHg or Systolic BP $\geq$200 mmHg) has been initiated at the time the participant's blood pressure was measured, a referral may take place during the Exit Interview.

b. Blood Chemistry Measurements

All 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 Visit 6 include serum total and HDL-cholesterol, serum triglycerides, serum glucose, serum creatinine, blood HbA1c, urine albumin and urine creatinine. The reference and alert values used by the central laboratories, summarized in Table 20.2, correspond to current recommendations by the National Cholesterol Education Program and national professional associations. Other assays performed on Visit 6 specimens are of research value only.

c. Otoscopy and Audiometry

Results from the otoscopy and audiometry performed at the ARIC field center or as a home visit examination are reported on site, following the examination. The results also are included in the consolidated report of study results mailed to study participants 6-8 weeks following the examination. Results make reference to excessive or impacted cerumen and hearing ability.

Table 20.2 ARIC-NCS Visit 6. 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 < 130 and DBP <80	Normal			Your blood pressure was normal. Please recheck it in two years. 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	Normal			Your blood pressure was high 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 140-159 or DBP 90-99		Abnormal		Your reading was elevated. At the time of your visit, we indicated that you should have your blood pressure checked within two months by a physician. 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 160-179 or DBP 100-109			Alert	Your reading was elevated. At the time of your visit, we indicated that you should have your blood pressure checked within a month by a physician.
Seated blood pressure	SBP 180-199 or DBP 110-119			Alert	Your reading was significantly elevated. At the time of your visit we indicated that you should see your physician within one week, to determine whether treatment should be started or changed. If you have not done so already, please see your physician soon.
Seated blood pressure	SBP >= 200 or DBP >=120			Alert; Stop Exam; Urgent referral	Your blood pressure reading was very high. At the time of your visit we indicated that you must see your physician at the earliest opportunity to confirm this finding. If you have not done so already, please see your physician at once.

Table 20.2 ARIC-NCS Visit 6. 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
Weight	Value	Can use 'Normal' cover letter			N/A
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
Waist circumference	N/A	Can use 'Normal' cover letter			The waist girth is a marker of fat deposited in the abdomen. Excess abdominal fat contributes to risk of disease.
The ankle-brachial index (ABI)	N/A	Can use 'Normal' cover letter			The ankle-brachial index (ABI) is the systolic blood pressure in the ankle divided by the systolic blood pressure in the arm. An ABI value less than 0.90 is strongly suggestive of a blockage of the arteries in the leg. An ABI value between 0.90 and 1.00 is considered borderline, and a value above 1.40 also may be abnormal. Any ABI outside the 1.00 to 1.40 range should be discussed with your health care provider, and may require additional testing.
Triglycerides	Triglyceride <220 mg/dl for a woman, Triglyceride < 250 mg/dl for a man	Normal			Your serum triglyceride is in the normal range.
Triglycerides	Triglyceride 220-999 mg/dl for a woman, Triglyceride 250-999 mg/dl for a man		Abnormal		Your serum triglyceride is high. You should check with your physician about this.
Triglycerides	Triglycerides >=1000mg/dl			Alert	Your serum triglyceride is very high. You should check with your physician about this as soon as possible.

Table 20.2 ARIC-NCS Visit 6. 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
Total cholesterol	Value	Can use 'Normal' cover letter			Total cholesterol levels less than 200 mg/dL are optimal
LDL-cholesterol (calculated)	Value	Can use 'Normal' cover letter			LDL-cholesterol values less than 100 mg/dL are optimal, 100-129 mg/dL are near or above optimal, 130-159 mg/dL are borderline high, 160-189 mg/dL are high. 190 mg/dL and above are very high.
HDL-cholesterol	Value	Can use 'Normal' cover letter			HDL-cholesterol values below 40 mg/dL are sub-optimal
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.
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.
Platelet count	150 – 450 $x10^9$/L	Normal			Platelet counts are usually in the range 150 to 450 x 109 $x10^9$/L. Platelet counts were measured using frozen whole blood and should be repeated in a fresh blood sample.

Table 20.2 ARIC-NCS Visit 6. 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
Platelet count	51 $x10^9$/L - 149 $x10^9$/L or 451 $x10^9$/L - 999 $x10^9$/L		Abnormal		Your platelet count is outside the normal range, which suggests that this exam should be repeated. Please check with your physician about this. Platelet counts were measured using frozen whole blood and should be repeated in a fresh blood sample.
Platelet count	<=50 $x10^9$/L or >=1000 $x10^9$/L			Alert	Your platelet count is markedly outside the normal range, which suggests that this exam should be repeated. Please check with your physician about this. Platelet counts were measured using frozen whole blood and should be repeated in a fresh blood sample.
Fasting glucose	Fasting glucose <100 mg/dl	Normal			Your fasting blood glucose is in the normal range.
Fasting glucose	Fasting glucose 100 – 125 mg/dl		Abnormal		Your fasting blood glucose is somewhat high. You may have a condition called pre-diabetes and should check with your physician about this at your next appointment. If you know that you have diabetes, please follow your physician's instructions.
Fasting glucose	Fasting glucose 126 – 399 mg/dl		Abnormal		Your fasting blood glucose is high. You should check with your physician about this.
Fasting glucose	Fasting glucose >=400 mg/dl			Alert	Your fasting blood glucose is very high. You should check with your physician about this as soon as possible.
Glycosylated hemoglobin	HbA1c	Can use 'Normal' cover letter			Normal A1C levels can be from 4.5 to 6% for someone who does not have diabetes. A result between 5.7 and 6.4% can indicate prediabetes (a high risk of developing diabetes). If you have 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

Table 20.2 ARIC-NCS Visit 6. 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
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 aspartate aminotransferase (AST)	AST (units per liter)	Can use 'Normal' cover letter			The usual range for AST is between 10 to 40 units per liter. Values 2-3 times greater can indicate damage to your liver.
Serum alanine aminotransferase (ALT)	ALT (units per liter)	Can use 'Normal' cover letter			The usual range for ALT is between 7 to 56 units per liter. Values 2-3 times greater can indicate damage to your liver.
Serum gamma-glutamyltransferase (GGT)	GGT (units per liter)	Can use 'Normal' cover letter			The usual range for GGT is between 0 to 51 units per liter. If elevated, it can suggest diseases of the liver or the pancreas
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) <= 2mg/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.

Table 20.2 ARIC-NCS Visit 6. 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
Serum creatinine	Creatinine (CR) > 2mg/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.
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.

Table 20.2 ARIC-NCS Visit 6. 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
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.
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
Audiometry	AUD1a indicates Excessive Cerumen (<50% eardrum visible) in right ear		Abnormal		Examination of your ears revealed that cerumen (or wax) in your right ear was excessive but did not completely block your ear canal. Please follow up with your healthcare provider.
Audiometry	AUD1b indicates Excessive Cerumen (<50% eardrum visible) in left ear		Abnormal		Examination of your ears revealed that cerumen (or wax) in your left ear was excessive but did not completely block your ear canal. Please follow up with your healthcare provider.
Audiometry	AUD1a indicates Impacted Cerumen (No visible eardrum) in right ear		Abnormal		Examination of your ears revealed impacted cerumen (or wax) in your right ear, completely blocking the ear canal. Please follow up with your healthcare provider.
Audiometry	AUD1b indicates Impacted Cerumen (No visible eardrum) in left ear		Abnormal		Examination of your ears revealed impacted cerumen (or wax) in your left ear, completely blocking the ear canal. Please follow up with your healthcare provider.
Audiometry	AUD1b Other Finding – left ear		Abnormal		Examination of your ear revealed a possible abnormal finding in your left ear. Please follow up with your healthcare provider.
Audiometry	AUD1a Other Finding – right ear		Abnormal		Examination of your ear revealed a possible abnormal finding in your right ear. Please follow up with your healthcare provider.

Table 20.2 ARIC-NCS Visit 6. 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
Audiometry	AUD1a Normal finding – right ear	Normal			Examination of your right ear showed a normal visible eardrum.
Audiometry	AUD1b Normal finding – left ear	Normal			Examination of your left ear showed a normal visible eardrum.
ZioPatch	ZDX1a = Wide QRS tachycardia >120 bpm and sustained for >30 seconds (includes monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, ventricular fibrillation)			Alert	This is a fast heart beat that originates from the lower chambers of the heart and may feel like palpitations or “racing heart beats”. Please follow up with your healthcare provider as soon as possible.
ZioPatch	ZDX1b = Complete heart block			Alert	This is a slow heart beat due to an interruption in the electrical pathway in the heart. Please follow up with your healthcare provider as soon as possible.
ZioPatch	ZDX1c = 2nd degree AV Block, Mobitz II			Alert	This is a slow heart beat due to an interruption in the electrical pathway in the heart. Please follow up with your healthcare provider as soon as possible.
ZioPatch	ZDX1d = Pause >6 seconds			Alert	There was no heart beat for 6 seconds or longer. Please follow up with your healthcare provider as soon as possible.
ZioPatch	ZDX1e = Bradycardia <40 bpm and sustained for >30 seconds			Alert	This is a slower than usual heart rate that lasted more than 30 seconds. Please follow up with your healthcare provider as soon as possible.
ZioPatch	ZDX1f = Atrial fibrillation/atrial flutter with average heart rate <40 bpm or >180 bpm and sustained for 60 seconds			Alert	This is an irregular heart rhythm. It may feel like palpitations or “racing heart beats”. Please follow up with your healthcare provider as soon as possible.
ZioPatch	ZDX1g = Narrow QRS tachycardia >180bpm and sustained for 60 seconds			Alert	This is a fast rhythm that originates from the upper chambers of the heart. It may feel like palpitations or “racing heart beats”. Please follow up with your healthcare provider.
ZioPatch	ZDX1h = yes			Alert	Other abnormalities deemed important by EPICARE

Table 20.2 ARIC-NCS Visit 6. 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
ZioPatch	ZDX2a = Atrial fibrillation		Abnormal		This is an irregular heart rhythm. It may feel like palpitations or “racing heart beats.” If you know that you have atrial fibrillation, please follow your physician's guidelines. Otherwise, please share these results with your physician.
ZioPatch	ZDX2b = Atrial flutter		Abnormal		This is a fast rhythm that originates from the upper chambers of the heart. It may feel like palpitations or “racing heart beats.” If you know that you have atrial flutter, please follow your physician's guidelines. Otherwise, please share these results with your physician.
ZioPatch	ZDX2c = Supraventricular ectopy (SVE) / Premature atrial contractions (PACs) / Supraventricular bigeminy / Supraventricular trigeminy / Supraventricular couplets / Supraventricular triplets		Abnormal		These are heartbeats that come early and originate from the upper chambers of the heart. They may feel like palpitations or “skipping a beat.”
ZioPatch	ZDX2d = Supraventricular tachycardia		Abnormal		This is a fast rhythm that originates from the upper chambers of the heart. It may feel like palpitations or “racing heart beats.”
ZioPatch	ZDX2e = Ventricular ectopy (VE) / Premature ventricular contractions (PVCs) / Ventricular bigeminy / Ventricular trigeminy / Ventricular couplets / Ventricular triplets		Abnormal		These are heartbeats that come early and originate from the lower chambers of the heart. They may feel like palpitations or “skipping a beat.”
ZioPatch	ZDX2f = Nonsustained ventricular tachycardia		Abnormal		This is a fast rhythm that originates from the lower chambers of the heart. It may feel like palpitations or “racing heart beats.”
ZioPatch	ZDX2g = 2nd degree AV block, Mobitz I (AV Wenkebach)		Abnormal		This is an occasional slowing of heart rate due to a drop of a beat in the lower heart chambers.

Table 20.2 ARIC-NCS Visit 6. 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
ZioPatch	ZDX2h = Paced beats		Abnormal		These are heart beats that originate from a pacemaker device rather than your heart's own pacemaker.
ZioPatch	ZDX2i = yes		Abnormal		Other abnormalities deemed important by EPICARE
ZioPatch	ZDX indicates no alerts or abnormalities	Normal			Your ZioPatch monitoring results are in the normal range.
Falls Risk	FRC13 >=4			Alert	Based on your responses, you are currently at an increased risk of falls. We strongly encourage you to take a copy of the questionnaire you completed to discuss with your physician during your next visit. Please also review the pamphlet on strategies to help identify and fix hazards in the home that increase risk of falls.
Falls Risk	FRC13 < 4	Normal			Based on your responses, you are currently at a low risk of falls. Please keep a copy of the questionnaire you completed and review the pamphlet on strategies to help identify and fix hazards in the home that increase risk of falls.
Peripheral Neuropathy Assessment	PNF item 4=N - Test failed	Not reported			<suppress report for either foot>
Periph. Neuropathy Assessment	PNF item 1=1 or 2 or 3 - Amputation of right foot	Not reported			<suppress statements for right foot>
Periph. Neuropathy Assessment	PNF item 3=R		Abnormal		The examination of your feet showed lesions on your right foot. If your physician is unaware of these lesions, please discuss these results with your provider of health care.
Periph. Neuropathy Assessment	PNF item 3=L		Abnormal		The examination of your feet showed lesions on your left foot. If your physician is unaware of these lesions, please discuss these results with your provider of health care.

Table 20.2 ARIC-NCS Visit 6. 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
Periph. Neuropathy Assessment	PNF item 3=B		Abnormal		The examination of your feet showed lesions on your right and left foot. If your physician is unaware of these lesions, please discuss these results with your provider of health care.
Periph. Neuropathy Assessment	PNF item 13=N	Normal			We examined your ability to feel light pressure on the bottom of your feet. This test showed that you have normal sensation in your right foot.
Periph. Neuropathy Assessment	PNF item 13=D		Abnormal		We examined your ability to feel light pressure on the bottom of your feet. This test showed that you have decreased sensation in you right foot. If your physician is unaware of this, please discuss these results with your provider of health care.
Periph. Neuropathy Assessment	PNF item 13=U	Normal			We examined your ability to feel light pressure on the bottom of your feet. We could not collect enough information to report your results on the right foot.
Periph. Neuropathy Assessment	PNF item 2=1 or 2 or 3 - Amputation of left foot	Not reported			<suppress statements for left foot>
Periph. Neuropathy Assessment	If PNF item 14 =N	Normal			We examined your ability to feel light pressure on the bottom of your feet. This test showed that you have normal sensation in your left foot.
Periph. Neuropathy Assessment	If PNF item 14 =D		Abnormal		We examined your ability to feel light pressure on the bottom of your feet. This test showed that you have decreased sensation in your left foot. If your physician is unaware of this, please discuss these results with your provider of health care.
Periph. Neuropathy Assessment	If PNF item 14 =U	Normal			We examined your ability to feel light pressure on the bottom of your feet. We could not collect enough information to report your results on the left foot.

Appendices

Appendices are identified by section number in Manual 2, and are found in the secure section of the ARIC study Website (https://www2.cscc.unc.edu/aric/)
under Cohort -> V6/NCS -> V6/NCS Manuals

Appendix 1.A. PROTOTYPE RECRUITMENT LETTER 2

Appendix 1.B. VISIT 6 SCHEDULING SCRIPT 3

Appendix 1.C. PROTOTYPE APPOINTMENT LETTER 6

Appendix 1.D. ARIC MEDICATION INSTRUCTIONS (to be included with the clinic packet) 8

Appendix 1.E. CLINIC APPOINTMENT REMINDER 9

Appendix 1.F. HOME APPOINTMENT REMINDER 10

Appendix 1.G. PROXY/INFORMANT RECRUITMENT 12

Appendix 2: ARIC NCS VISIT 6 EXAM CHECKLIST 14

Appendix 3: PROTOTYPE COVER LETTERS AND INSTRUCTIONS FOR REPORTING OF STUDY RESULTS 15

A. Reporting of ARIC Study Results and Alert Notifications – ARIC-NCS Visit 6 15

B. MD Letter: Alert Referral at Clinic Visit 17

C. MD Letter: Alert Referral After the Exam Visit 17

D. Alert – Participant: MD Designated 19

E. Alert – Participant: No MD Designated 20

F. Physician: Abnormal Results, No Previous Alert Reported 21

G. Physician: Abnormal Results, Previous Alert Reported 22

H. Physician: Normal Results 23

I. Participant: Normal Results, MD Designated 24

J. Participant: Abnormal Results, MD Designated 25

K. Participant: Abnormal Results, No MD Designated 26

L. Participant: Normal Results, No MD Designated 27

Appendix 4: Template – CES-D Alert Letter (Visit 6) 28

Appendix 5.A: Results Letter Template – Typical 29

Appendix 5.B: Results Letter Template – Atypical 30

Appendix 5.C: Results Letter Template – Undetermined 31

Appendix 1.A. PROTOTYPE RECRUITMENT LETTER

The ARIC Study / Logo
Street address
Town/city, State, Zipcode
Phone, number

Name of ARIC participant
Street address
Town/city, State, Zipcode

Dear <title> <name>:

It has been over 3 years since the Atherosclerosis Risk in Communities (ARIC) Study examined participants recruited in the late 1980s. We are very pleased to be able to now invite you back to the ARIC center for a 6th examination. The focus of this new exam will be on important areas of health research: the brain, the heart, and the senses. In this new ARIC exam we will conduct tests of your sense of smell and hearing, and of your touch. We will also conduct interviews to understand the ways blood flow to the brain sustains memory and will perform a test to study the rhythm of your heart. We will ask you to wear a Band-Aid-like device on your chest that will record the rhythm of your heart for up to two weeks. You may be also invited to participate in a study that explores how being physically active affects the risk of falling and be asked to use a small wearable device that records your physical activity.

ARIC staff will be calling you within a few days to conduct your usual annual phone interview and to determine your availability for this new visit. We ask you, if possible, to have a calendar available to facilitate scheduling of the new visit. If you prefer, feel free to call the ARIC telephone number listed above to ask our study staff any questions in advance, or to mention any concerns that you may have.

We appreciate your past participation in ARIC and hope you will choose to volunteer for this upcoming exam.

Sincerely,

[Principal Investigator]

Appendix 1.B. VISIT 6 SCHEDULING SCRIPT

Recruitment for visit 6 will usually be done in the context of AFU calls. Outcome of the recruitment call should be recorded in the Recruitment Tracking and Scheduling (RTS) form. After the corresponding AFU script, continue with the following:

"Next, I want to tell you about a new ARIC examination at the University of [XXX]. As we mentioned in the letter we mailed to you, we are now recruiting and scheduling people to be part of this new exam focused on heart disease and memory.

This ARIC clinic visit will be similar to previous visits, and will take place at the University of [XXX]. We expect it will take 4 to 5 hours, beginning in the morning. You will need to fast 8 hours unless you have a medical reason to not fast. We will reimburse you for your travel, or we can provide taxi services. In addition, we will give you a monetary compensation for your participation in this visit. Our appointment times are at [TIMES]. Is there a day or time that would be best for you?"

1. If appointment is scheduled, record the date and time read the following, and skip to 5 (special needs assessment).

We will be mailing an instruction brochure to you. We also will give you a reminder call the day before your scheduled visit.

1a. If respondent is unable to schedule appointment at this time, indicate on record of calls, specify reason and prospects for recontacting, and skip to CLOSING (section 6).

2. If respondent is unwilling to schedule a clinic visit, ask the participant about reasons for not participating:

"Is there a specific reason you are not willing to participate in this ARIC visit?"

[Do not read responses unless the participant does not offer a reason]

a. Too busy? Highlight that the participant will receive a number of different tests including an hearing test and a comprehensive cognitive assessment. If still does not agree to complete full exam, see 3 below

b. Exam requires too much time? Highlight that the participant will receive a number of different tests including a hearing test and a comprehensive cognitive assessment. If still does not agree to complete full exam, see 3 below

c. Not interested? Highlight the value of the knowledge that will be gained from the study. Try to work out a way that it will work.

d. Fearful of study procedures? Read the following: **"All the examinations done by ARIC are considered safe. Some tests can cause minor discomfort, but you can always withdraw from the study at any moment without negative consequences. Do you have any additional concern?"** Answer questions from the participants. If the participant agrees, go back to section 1 and schedule appointment.

e. Because of their, or a family member's, health? See 4 below

f. Unable to travel? See 4 below

g. Distance **"We might schedule the appointment at some other time, before the end of the study, when you are in the area. Do you expect to come back to the area before December 2017?"** If YES, try to schedule a follow-up call closer to the date or schedule visit. If NOT, try to negotiate travel arrangements. Another possibility is a visit to another ARIC field center.

h. Another reason? Try to work out a way that it will work.

3. If participant is unwilling to participate because he or she is too busy or the exam seems too long, we can offer him or her an abbreviated clinic exam that will take approximately 3 hours:

"We understand that 4-5 hours is a long visit. Would you be willing to complete an abbreviated clinic visit which will last approximately 3 hours?"

If NO, go to section 4.

If YES, offer dates and times, schedule abbreviated clinic exam appointment, read the following and skip to section 5 (Special Needs Assessment).

"We will be mailing an instruction brochure to you. We also will give you a reminder call the day before your scheduled visit"

4. If the participant is unable to participate due to illness, residing in a long-term care facility (LTCF), or any inability to come to the clinic, we will offer the opportunity of an abbreviated exam (<3 hours) at the participant's home or nursing home.

"Even if you cannot or prefer not to participate in the clinic exam, we would be happy to come to your home (or current residence [if at LTCF]) and conduct an abbreviated exam there."

If participant does not agree to home visit, go to section 6 (closing).

If the participant agrees to home visit, proceed to schedule an appointment, or make arrangements for a call back to do this. This might involve scheduling a joint appointment with an exam proxy:

"We will be mailing an instruction brochure to you. We also will give you a reminder call the day before your scheduled visit."

5. Special needs assessment and safety screening

At the time of recruitment, it will be necessary to assess the participant's transportation and special needs. Also, if the visit is scheduled soon after the recruitment call (<2 weeks), the Participant Safety Screening (PSA) form could be administered. If the PSA form is not administered during the recruitment call, then it could be administered during the appointment reminder call or at the clinic visit.

5a. If exam is going to be conducted at the field center, read the following:

"To help us prepare for your visit to the ARIC center:"

"Do you need assistance in arranging for transportation?"

If YES, discuss transportation options and arrangements with participant.

"Do you need any kind of assistance reading, hearing questions, walking or in getting on an examination table?"

If YES, record the specific need in item 5 of RTS form.

At the discretion of the recruiter, the safety screening could be administered now, and answers recorded in the PSA form. If not administered now, the safety screening can be administered during the reminder call or at the time of the clinic exam. Then, go to CLOSING (6).

5b. If exam is going to be conducted at the participant's home or in a LTCF, read the following:

"To help us prepare for our visit to [your home /residence]:"

"Do you have a quiet room that has a table and at least two chairs that we can meet in?"

"Will there be anyone there with you during our visit?"

If YES:

"How many persons?" "Would that/those person(s) be a spouse?" "Caretaker?" "Your proxy?" "Other?"

"Would any person(s) be dependent upon you for their care?"

If YES to previous question:

"Would someone else be able to provide their care while we are in your home?"

Only if exam is scheduled conducted at the participant's home ask the following:

"Do you have pets?"

If YES:

"So that we aren't interrupted, would it be possible to put your pets in another room while we complete the home visit?"

At the discretion of the recruiter, the safety screening could be administered now, and answers recorded in the PSA form. If not administered now, the safety screening can be administered during the reminder call or at the time of the home exam. Then, go to CLOSING (6).

6. Closing

"We want to thank you for your time today. We look forward to talking with you at your next ARIC telephone interview. Good-bye"

Appendix 1.C. PROTOTYPE APPOINTMENT LETTER

Dear [NAME],

Thank you for agreeing to participate in the new exam in the ARIC Study. Your appointment has been scheduled for:

Day_____ Date _____ Time _____

It is expected to take 4-5 hours.

[If the participant agreed to use his/her own car, no need to include the following]

A taxi will pick you up at your home at approximately _____ and will return you to your home after the exam. Please read the following instructions carefully:

- FASTING

You should fast for 8 hours before your appointment time. A snack will be provided during your visit. Please drink several extra glasses of water on the night before your exam. This will make obtaining your blood samples easier. Also, please drink a glass or two of water first thing in the morning of your visit.

- SMOKING AND PHYSICAL ACTIVITY

Please refrain from smoking or vigorous physical activity at least one hour before your appointment

- CLOTHING

You may be asked to remove your upper body clothing (except bras). Please wear loose clothes that are easily removed and comfortable shoes or slippers that are easy to take on and off. Please leave necklaces at home. Also, we suggest you do not use perfume or body lotion.

- MEDICATIONS

Please be sure to bring your medications in their <u>original</u> containers. You should put these containers in the ARIC medication bag.

- GLASSES AND HEARING AIDS

If you normally use glasses for reading, please bring them with you to the clinic. Also, bring your hearing aids, with fresh batteries, if you use them.

- PHYSICIAN CONTACT

Please complete the form on back of the Medications Instructions and bring it with you to the clinic.

- DOCUMENTS

Please bring your Medicare card to the examination. As you know, ARIC is identifying medical events in its participants, and the Medicare number helps ARIC obtain health care information. Your Medicare number and any information obtained are treated with the utmost confidentiality.

- TAKING YOUR MEDICATIONS ON THE DAY OF THE ARIC EXAM

If you are taking daily medications, please do the following on the day of your ARIC examination, or consult with your physician if you are in doubt:

- <u>Medications to lower you blood pressure</u>: please take these medications according your usual schedule.

- Medications for angina: take these on the day of the examination according to your usual schedule.
- If you have diabetes and take insulin or oral medications to lower your blood sugar you can postpone taking them until the blood draw at the ARIC center, and the snack.
- There are no particular concerns about taking aspirin or blood thinners.
- All other medications should be taken as prescribed by your physician. Some of these medications may need to be taken with food, and at set times. Please let the ARIC staff know when and how you need to take these medications. If any adjustments need to be made, please consult with your physician.

Please remember to bring the medications you need to take during the day with you to the ARIC center and let us know of any that need to be kept refrigerated.

To help you to move through the clinic on schedule, it is more important that you be on time for your appointment.

If you have any question or a problem with your appointment, please call the clinic at [PHONE NUMBER] between [7:30 a.m.] and [4:30 p.m.] Monday through Friday.

We look forward to seeing you again.

The ARIC Staff

Appendix 1.D. ARIC MEDICATION INSTRUCTIONS (to be included with the clinic packet)

During your visit to the Clinic, we would like to record any medicines you are taking because they tell us about a person's health and may have effects on the tests which we will perform.

We are interested in ALL medicines that you take for ANY reason, now or in the FOUR WEEKS before your visits to the ARIC clinic, not just in heart medicines. We ask you to assemble and bring to the ARIC center all your prescription, over-the-counter, and research medications. This includes 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

The best way to get this information is for you to bring in the provided medications bag the containers of any medicine used in the four weeks before your visit, including:

- Prescription drugs from your physician or dentist;
- Prescription drugs you may have received from other people, including friends or relatives;
- Non-prescription medicines (over the counter) that you obtained from a drug store, supermarket, by mail, or from the internet, such as aspirin, cold remedies, allergy medications, vitamins, minerals, supplements, or the like.

In order to be sure you have included everything, think about the past few weeks when you were ill, when you visited a physician or dentist and might have been given medication.

We ask that you bring the containers so that we can copy information from the label. If you don't have the container, please bring the prescription or any other information that has the name of the drugs. Even if you only have loose pills or capsules, please bring them to the clinic so that we can identify them.

At the clinic we will handle all your medicines and containers very carefully and will return them in the same bag before you leave. Like all other information we collect, your use of medicines will be kept in strict confidence.

We will provide your doctor(s) with results of your tests if you would like us to. Will you please fill out the information below and bring it with you to the clinic so that we will not have to take time during the clinic visit to look up the information?

Primary doctor:

_____

YOUR DOCTOR'S / CLINIC NAME

_____

STREET ADDRESS

_____

CITY STATE ZIP CODE

_____

TELEPHONE NUMBER

Appendix 1.E. CLINIC APPOINTMENT REMINDER

1. Opening and instructions about fasting:

"Hi, this is __(NAME)__, with the ARIC study at [INSTITUTION]. May I please speak with [Participant's Name]? I am calling to remind you of your clinic appointment on [DATE] at [TIME]. We look forward to seeing you tomorrow. Also, we would also like to remind you about some additional items that were included in the information package we sent you."

Go over the different items in the appointment letter, including transportation arrangements, if any were done, length of exam, need to bring glasses, comfortable clothing, physician information, and need to avoid smoking and vigorous physical activity.

"In addition, for this visit, we ask you to fast prior to the exam unless you are unable due to medical reasons. Do you take insulin or other medication for diabetes or have any other reason that you cannot fast for 8 hours?"

If YES: **"We would like for you to fast for 8 hours before the visit, unless your doctor has prescribed a bedtime snack, and come to the clinic without taking your morning insulin or other diabetes medication. Once we have completed the procedures that require fasting, we will give you breakfast at the clinic, and you can take your diabetes medication. Fasting means nothing by mouth but water and essential medications. We do encourage you to drink water. If you have any concerns about fasting or your diabetes medication, we encourage you to contact your physician."** Go to **2**.

If NO: **"Since your appointment is at [TIME], you should begin fasting the night before at [TIME]. Fasting means nothing by mouth but water and essential medications. We do encourage you to drink water. You will be given a snack at the clinic."** Go to **2**.

2. Reminder about need to bring medicines

"We will ask you about your use of medicines, vitamins or supplements. This includes all medicines such as prescription drugs from all doctors, prescription drugs you may have received from other people, such as friends or relatives, over the counter medications, such as medicines for colds, vitamins, minerals, or other supplements. ARIC is interested in 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.

We ask that you bring the containers so that we can copy information from the labels. Please bring in the bottles of any medication you have taken in the PAST FOUR WEEKS. If you do not have the container, please bring the prescription or the loose pills or capsules. A bag to carry your medications was included in the packet that was mailed to you. Do you have any questions about this or any other aspect of your clinic visit?"

If questions, address them. Then, go to **4** (Closing).

3. Patient Safety Screening

If not administered during the recruitment call, the safety screening could be administered during this call (PSA form).

4. Closing

"We look forward to seeing you tomorrow"

Appendix 1.F. HOME APPOINTMENT REMINDER

If talking with proxy instead of participant, adapt as needed.

1. Opening and instructions about fasting:

"Hi, this is __[NAME]_, with the ARIC study at [INSTITUTION]. May I speak with [Participant's name]? I am calling you to remind you of your visit on [DATE] at [TIME]. We look forward to seeing you tomorrow."

Go over the different items in the appointment letter, including length of exam, need to have a table and two chairs, comfortable clothing, need to have readily available physician information, and need to avoid smoking and vigorous physical activity.

"For this visit, we ask you to fast prior to the exam unless you are unable due to medical reasons. Do you take insulin or other medication for diabetes or have any other reason that you cannot fast for 8 hours?"

If YES:

"We would like for you to fast for 8 hours before the visit, unless your doctor has prescribed a bedtime snack, and to not take your morning insulin or other diabetic medication. After we complete the procedures that require fasting, you could have breakfast and take your diabetes medication. Fasting means nothing by mouth but water and essential medications. We do encourage you to drink water. If you have any concerns about fasting or your diabetes medication, we encourage you to contact your physician." Go to **2**.

If NO and appointment in the morning:

"Since your appointment is at [TIME], you should begin fasting the night before at [TIME]. Fasting means nothing by mouth but water and essential medications. We do encourage you to drink plenty of water." Go to **2**.

If NO and appointment in the afternoon:

"Since your appointment is at [TIME], we understand that it might not be possible to fast for 8 hours. In any case, we would like you to fast after breakfast. Fasting means nothing by mouth but water and essential medications. We do encourage you to drink plenty of water." Go to **2**.

2. ONLY for individuals at nursing homes, read the following paragraph. Adapt as needed if arrangements are being made with nursing home staff:

"We understand that fasting might be difficult in your situation. We encourage you to make arrangements with your caregivers, if possible. We will bring snacks for participants who are fasting."

Read the following to ALL (home or nursing home):

"We will ask you about your use of medicines, vitamins or supplements. This includes all medicines, such as prescription drugs from all doctors, prescription drugs you may have received from other people, such as friends or relatives, over the counter medications, such as medicines for colds, vitamins, minerals. We ask that you have the containers available so that we can copy information from the labels. If you don't have the container, please show us the prescription or the loose pills or capsules. A bag to put them in is in the packet that was mailed to you. Do you have any questions?"

If questions, address them. Participants in nursing homes or assisted living facilities most likely will not have their own medication. In that case, it will be necessary to obtain this information from the caregivers at the facility.

If a proxy or informant will be present, according to results from the recruitment call, read the following:

“In our initial call, you mentioned that [PROXY/INFORMANT NAME] will also be present during our visit. Is this still the case?”

Keep track of proxy/informant availability.

4. Closing

“We look forward to seeing you on [DATE].”

Appendix 1.G. PROXY/INFORMANT RECRUITMENT

Information collected as part of this call is collected in the Recruitment Tracking and Scheduling (RTS) Form, for those circumstances in which a proxy is required to accompany the participant to the visit.

1. "Hi, may I talk with [PROXY'S NAME]? My name is [NAME] and I am with the ARIC Study, a clinical research study being conducted by [INSTITUTION]. The study aims to understand the health of the heart and the brain. I am contacting you on behalf of [Mr./Ms.] [PARTICIPANT'S NAME], who has been a participant of the ARIC study for over 25 years. [HE/SHE] is interested in being involved in a new exam in the study and has provided your name as a proxy, who might help [HIM/HER] to make decisions about study participation. Is this a good moment to talk with you?"

If NO:

"When would be a good time to call you back?"

Record and reschedule call. Go to **CLOSING**.

If YES:

2. "[Mr./Ms.] [PARTICIPANT'S NAME] has shown interest in being involved in a new exam as part of the ARIC study. [HE/SHE] has agreed to [come to our clinic/have us go to his/her residence or care facility] for this exam on [DATE/TIME]. However, [HE/SHE] may need help to make decisions about participation. Would you be willing to help in this role?"

If YES:

"We will mail you information about the ARIC exam and information on the date and time of the visit. You might want to contact [Mr./Ms.] [PARTICIPANT'S NAME] to coordinate the exam with [HIM/HER]. Do you have any questions?"

2a. If YES, address questions, and then go to **CLOSING**. If NO, go to **CLOSING**.

If NO:

"Is there a specific reason you are not willing to participate as a proxy in this ARIC visit?"

[Do not read responses unless the participant does not offer a reason]

a. *Too busy?* → Highlight that the time commitment will be limited to this exam and the importance of the knowledge to be gained from this research.
b. *Not interested?* → Point out the interest of the ARIC participant and the important role the proxy plays.
c. *Unable to travel? Distance?* → Explain that arrangements have been made with the study participant to facilitate transportation to the field center.
d. *Not an adequate proxy* → Ask about other person who could be a better proxy for the participant.
e. *Another reason?* → Try to work out a way that it will work.

If need be, consult with your supervisor.

3. Closing

"I would like to thank you again for your time. Good-bye."

Appendix 1.H. NAME AND CONTACT INFORMATION FOR SCHEDULING OF ARIC PARTICIPANTS IN ALTERNATE FIELD CENTERS

Forsyth County

Josh Evans

PP I 1st floor Suite 101
1920 W 1st st
Winston Salem, NC 27104

Phone: 336-716-7282. Email: josevans@wakehealth.edu

Jackson

Stacee Naylor

University of Mississippi Medical Center
Office Annex II
2500 North State St.
Jackson, MS 39213

Phone: 601-984-6649. Email: sbnaylor@umc.edu

Minnesota

Nancy McCreary

University of Minnesota
Epidemiology Clinical Research Center
1100 Washington Ave. South Suite 201
Minneapolis, MN 55415

Phone: 612-624-8914. Fax: 612-626-6983. Email: nmccrear@umn.edu

Washington County

Melissa Minotti

The Johns Hopkins University
1100 Dual Highway
Hagerstown, MD 21740

Phone: (301) 791-1847. Fax: (301) 791-3541. Email: mminott@jhu.edu

Appendix 2: ARIC NCS VISIT 6 EXAM CHECKLIST

Name: _____ Visit Date/Time: _____

ID Number: _____ DOB: _____

Transportation: Drive ☐ Taxi Pick-up Time

Participant wants forms read to them? YES NO

Diabetic? Y N	Will need medications Y N	Needle safety explained Y N	Medical support needed Y N	Tanita Exclude: Y N	Pre-Selected For Falls? Y N	ZioPatch ? Y N	Notes:

Start Time	End Time	Excluded/ Refused	Procedure/Form	Staff ID
			Consent ☐[1] Proxy Consent ☐[1] HIPPA ☐[1]	
			Update/Safety/IC tracking: CIU ☐[1], PSA ☐[1], MSR ☐[2], ICT ☐[1]	
			Sitting Blood Pressure (SBP) [1]	
			Anthropometry: Weight [1], Tanita, waist measurement (ANT)	
			Blood draw: Fasting ☐[1] (BIO) Urine Collection ☐[1]	
			Snack[1]	
			Cognitive Testing	
			Block A[1,4] , Neurologic Hx (NHX) ☐[3], Depression (CES) ☐	
			Break	
			Block B[4] and Neurocog Summary Score (NCS)	
			Hearing Test[3] : (AUD, HHI, HNE)	
			Lunch	
			Physical Function Tests (PFX)	
			Peripheral Neuropathy Testing (PNF)	
			Interviews-- CDR Participant (CDP)[1]	
			(If needed) CDR Informant (CDI), CDR Summary (CDS), NPI ☐	
			Personal History (PHX)[2]	
			Medication Survey (MSR)[2]	
			Smoking and Alcohol Use (ALC)[2]	
			SF-12 Health Survey (SFE) [2]	
			Two Minute Walk (TMW)	
			Interviews-- Epworth Sleepiness Scale (ESS)[3]	
			Physical Abilities (PAQ)	
			Physical Activity Questionnaire (PAC)	
			Diabetics only: Diabetes Questions (DQF)	
			General Preventive Care (DTS)	
			ZioPatch[3]	
			PA and Falls Study (Consent, FES, FRM, STEADI→FRC)	
			Accelerometer placement and instructions (FCL,FCF)	
			End of Visit Review[1]--Go over Summary of Results report	
			Participant confirms receipt of medication bag ☐[1]	
			Stage 2 call—Cognitive Status Informant interview (CDI)	

Eligible for Falls? Y N	Selected for Stage 2 Y N	
		1—Abbreviated Exam Priority 1 2—Abbreviated Exam Priority 2 3—Abbreviated Exam Priority 3 4—Ppts diagnosed with dementia at V5 will only do Cognitive Testing Block A

Appendix 3: PROTOTYPE COVER LETTERS AND INSTRUCTIONS FOR REPORTING OF STUDY RESULTS

A. Reporting of ARIC Study Results and Alert Notifications – ARIC-NCS Visit 6

Overview

a. Retrieve the template cover letters from the ARIC study website (https://www2.cscc.unc.edu/aric/v6-ncs-docs) and store them in a folder on your computer, so you can access them to generate alert letters and ARIC results cover letters to participants and their physicians. An overview table listing these 11 template letters is shown below and is included on the website with the letters.

b. Check the study website daily for alert reports, and look regularly at the V6 *Results Status Report* to see what results are due and available for your participants.

c. Print the participant's report of results from CDART. Print the ZioPatch results from CDART to append to the results. Both may be accessed via the V6 *Results Status Report*.

d. Select the template appropriate letter (see table below).

e. CDART does not track who the results should be reported to, but the Alerts Report indicates whether or not the ppt. has given permission to release results. The CIU has a field for request to send results to physician (Q27) and if so, the physician's address.

f. Merge the names and addresses of the MD and participant into the template cover letters. Use the V6 Address Labels Report for participant addresses.

g. When all results are available to report for a participant, or delays require sending a partial report, check CIU Q27-29 to see who (participant, MD, proxy, etc.) should get the report of ARIC results.

Alert Reporting

1. Check daily for alerts.

2. Select the appropriate notification letter (e.g., MD designated, referral at the time of the exam visit, after the exam visit).

3. For each alert, look up the script in the results report or Table 20.1 of MOP 2 that describes the alert. This information needs to be included in the alert notification letter or conveyed by phone.

4. Consider whether this alert might already be known and might not need to be treated as an alert (e.g., longstanding atrial fibrillation on treatment need not be an alert).

5. Determine from the Alerts Report or CIU Q27-29 to whom the participant wanted results sent.

6. Discuss items 3-4 with your field center MD or clinician, per local protocol. Determine whether the alert reporting should be done by letter or whether a phone call is needed. You may bypass field center MD consultation if rules are set up with the MD on how to handle various alerts.

7. Generate and send alert letters, or make phone calls followed by letter.

8. Record this action on the RAR form.

Results Reporting

1. Print the participant's report of results from CDART. Print the ZioPatch results from CDART to append to the results. Both may be accessed via the V6 *Results Status Report*.

2. Check on the Alerts Report whether the ppt. has given permission to release results. The CIU has a field for request to send results to physician (Q27) and if so, the physician's address.

3. Check whether any results in this report are abnormal (abnormal values are listed in Table 20.2, include as an appendix in MOP 2).

4. Select the appropriate cover letter (e.g., participant, physician, are any results in this report abnormal, was an alert referred previously?).

5. Merge the names and addresses of the MD and participant into the template cover letters (see Overview).

6. Edit the letters as needed (e.g., explain why some results are missing; point out any special instructions; if applicable, explain to participant which MD got letter, etc.).

7. Have someone review the letters and reports to make sure there aren't errors.

8. Print and send the appropriate letters, envelopes, and reports.

9. Archive PDFs of letters, being certain to use the participant ID in naming the PDFs.

10. If only partial results were sent, repeat the process after the remaining results are available.

11. Record these actions on the RAR form.

Template Letters to Report Alert Results– ARIC-NCS Visit 6

Alerts	To ARIC Participant	MD Designated	Consider: Phone call and/or letter?
		No MD Designated	Consider: Phone call and/or letter?
	To Provider of Care	Referral at V6	--
		Referral after V6	--

Template Letters to Report Study Results– ARIC-NCS Visit 6

Results	To Participant	Normal Results	MD Designated	--
			No MD Designated	--
		Abnormal Results	MD Designated	--
			No MD Designated	Phone call?
	To Provider of Care	Normal Results	--	--
		Abnormal Results	No Previous Alert	--
			Previous Alert	--

B. MD Letter: Alert Referral at Clinic Visit

[Date]

[MD Name]
[Address]

RE: [Participant Name]
[Date of Birth]

Dear Dr. [MD Name]:

We saw your patient, [Participant Name], in the ARIC Study center on [Date]. During the course of our evaluation, the following problems were identified which we believe need attention:

[Insert alert report]

The ARIC Study does not provide diagnoses, medical advice, or treatment. We have recommended to [Participant Name] that [he/she] contact you as soon as possible to determine how to follow-up on these results.

Should you have any questions, please feel free to contact us at xxx-xxx-xxxx. A full report with results of our tests will be forwarded when available.

Sincerely,

_____
Principal Investigator

/xx

C. MD Letter: Alert Referral After the Exam Visit

[Date]

[MD Name]

[Address]

RE: [Participant Name]

[Date of Birth]

Dear Dr. [MD Name]:

We saw your patient, [Participant Name], in the ARIC Study center on [Date]. We have since received some results on your patient from our central laboratories. They include a finding which we believe needs attention.

[Insert alert report]

The ARIC Study does not provide diagnoses, medical advice, or treatment. We have recommended to [Participant Name] that [he/she] contact you as soon as possible to determine how to follow-up on these results.

Should you have any questions, please feel free to contact us at xxx-xxx-xxxx. A full report with results of our tests will be forwarded when available.

Sincerely,

_____

Principal Investigator

/xx

D. Alert – Participant: MD Designated

[Date]

[Participant Name]

[Address]

Dear [Mr./Mrs. Participant Name]:

Thank you for taking part in the ARIC Study examination at our Field Center. We appreciate your willingness to join us in this important study.

We have identified a result that seems abnormal that should be reviewed by a physician to be confirmed or studied further. This result is as follows:

[insert from alert report]

We encourage you to consult your physician or usual source of medical care, as soon as possible about this [result/these results]. Since you authorized us to share your study results with your physician we are sending a copy of this letter to the provider of medical care you designated

Our staff will continue to call you twice every year to stay in touch. Thank you again for being a member of the ARIC Study.

Sincerely,

_____

Principal Investigator

/xx

Attachment

E. Alert – Participant: No MD Designated

[Date]

[Participant Name]

[Address]

Dear [Mr./Mrs. Participant Name]:

Thank you for taking part in the ARIC Study examination at our Field Center. We appreciate your willingness to join us in this important study.

We have identified a result that seems abnormal that should be reviewed by a physician to be confirmed or studied further. This result is as follows:

[insert from alert report]

During your ARIC Study visit you indicated that we should send these results to you. We encourage you to consult your physician or usual source of medical care, as soon as possible about this [result/these results]. If you do not have a personal physician or do not know where to find one, we will assist you in finding one.

Our staff will continue to call you twice every year to stay in touch. Thank you again for being a member of the ARIC Study.

Sincerely,

_____

Principal Investigator

/xx

Attachment

F. Physician: Abnormal Results, No Previous Alert Reported

[Date]

[MD Name]

[Address]

RE: [Participant Name]

[Date of Birth]

Dear Dr. [MD Name]:

[Participant Name], a patient of yours, is a participant in the ARIC Study and was seen at our Field Center on [Date]. Attached to this letter is a report of the results of this examination. We have indicated on the report the results we consider to be outside the normal range.

The ARIC Study routinely offers to send all clinically relevant data to the participant's physician. Your patient has indicated that we should send these results to you. We also mailed a letter to your patient to report that one or more abnormal findings were noted during the ARIC Study examination and reported to you. We have also suggested that your patient contact you to determine if these findings need further study.

The ARIC Study examination procedures are designed exclusively for epidemiologic research. Our study procedures do not substitute for a clinical examination, nor does the study provide any diagnosis or treatment. If a condition or laboratory test result is found that requires diagnostic confirmation or possible treatment, the study participant is referred to his/her usual source of medical care.

Thank you for your cooperation.

Sincerely,

_____

Principal Investigator

/xx

Attachment

G. Physician: Abnormal Results, Previous Alert Reported

[Date]

[MD Name]

[Address]

RE: [Participant Name]

[Date of Birth]

Dear Dr. [MD Name]:

[Participant Name], a patient of yours, is a participant in the ARIC Study and was seen at our Field Center on [Date]. Attached to this letter is our final report of the results of this examination. We have indicated on the report the results we consider to be outside the normal range.

The ARIC Study routinely offers to send all clinically relevant data to the participant's physician. Your patient has indicated that we should send these results to you, and we have already reported to you about [the previous referral]. We are now sending a final report indicating possible abnormal findings to your patient, reminding him/her to contact you if he/she has not already done so.

The ARIC Study examination procedures are designed exclusively for epidemiologic research. Our study procedures do not substitute for a clinical examination, nor does the study provide any diagnosis or treatment. If a condition or laboratory test result is found that requires diagnostic confirmation or possible treatment, the study participant is referred to his/her usual source of medical care.

Thank you for your cooperation.

Sincerely,

_____

Principal Investigator

/xx

Attachment

H. Physician: Normal Results

[Date]

[MD Name]

[Address]

RE: [Participant Name]

[Date of Birth]

Dear Dr. [MD Name]:

[Participant Name], a patient of yours, is a participant in the ARIC Study and was seen at our Field Center on [Date]. Attached to this letter is a report of the results of this examination.

The ARIC Study routinely offers to send all clinically relevant data to the participant's physician. Your patient has indicated that we should send these results to you. We also mailed a letter to your patient to report that no abnormalities were found for any items covered by the ARIC Study examination, and that the enclosed results were sent to you.

The ARIC Study examination procedures are designed exclusively for epidemiologic research. Our study procedures do not substitute for a clinical examination, nor does the study provide any diagnosis or treatment. If a condition or laboratory test result is found that requires diagnostic confirmation or possible treatment, the study participant is referred to his/her usual source of medical care.

Thank you for your cooperation.

Sincerely,

_____

Principal Investigator

/xx

Attachment

I. Participant: Normal Results, MD Designated

[Date]

[Participant Name]

[Address]

Dear [Mr./Mrs. Participant Name]:

Thank you for taking part in the ARIC Study examination at our Field Center. We appreciate your willingness to join us in this important study.

The results of your examination are summarized on the attached sheet. Because the ARIC Study does not provide any clinical diagnosis or treatment, we offer to send all relevant information to participants' usual sources of medical care. As you instructed us to do during your ARIC Study visit we sent a copy of these results to [your provider of medical care / to Dr. Name]. We encourage you to review these results with your physician or usual source of medical care at the next convenient opportunity.

Our staff will continue to call you twice every year to stay in touch. Thank you again for being a member of the ARIC Study.

Sincerely,

_____

Principal Investigator

/xx

Attachment

J. Participant: Abnormal Results, MD Designated

[Date]

[Participant Name]

[Address]

Dear [Mr./Mrs. Participant Name]:

Thank you for taking part in the ARIC Study examination at our Field Center. We appreciate your willingness to join us in this important study.

The results of your examination are summarized on the attached sheet. We have identified the results which are possibly abnormal. In most instances such a result does not mean that a medical problem exists. However, we believe that the enclosed report should be reviewed by a physician to determine whether these results should be confirmed or studied further.

Because the ARIC Study does not provide any clinical diagnosis or treatment, we offer to send all relevant information to participants' usual sources of medical care. As you instructed us to do during your ARIC Study visit we sent a copy of these results to [your provider of medical care / to Dr. Name]. We encourage you to consult your physician or usual source of medical care, to review those results that we have highlighted for verification.

Our staff will continue to call you twice every year to stay in touch. Thank you again for being a member of the ARIC Study.

Sincerely,

_____

Principal Investigator

/xx

Attachment

K. Participant: Abnormal Results, No MD Designated

[Date]

[Participant Name]

[Address]

Dear [Mr./Mrs. Participant Name]:

Thank you for taking part in the ARIC Study examination at our Field Center. We appreciate your willingness to join us in this important study.

The results of your examination are summarized on the attached sheet. We have identified the results which are possibly abnormal. In most instances such a result does not mean that a medical problem exists. However, we believe that the enclosed report should be reviewed by a physician to determine whether these results should be confirmed or studied further.

Because the ARIC Study does not provide any clinical diagnosis or treatment, we offer to send all relevant information to participants' usual sources of medical care. During your ARIC Study visit you indicated that we should send these results to you. We encourage you to consult your physician or usual source of medical care, to alert them to those results that we have highlighted for verification. If you do not have a personal physician or do not know where to find one, please call us.

Our staff will continue to call you twice every year to stay in touch. Thank you again for being a member of the ARIC Study.

Sincerely,

_____

Principal Investigator

/xx

Attachment

L. Participant: Normal Results, No MD Designated

[Date]

[Participant Name]

[Address]

Dear [Mr./Mrs. Participant Name]:

Thank you for taking part in the ARIC Study examination at our Field Center. We appreciate your willingness to join us in this important study.

The results of your examination are summarized on the attached sheet. Because the ARIC Study does not provide any clinical diagnosis or treatment, we offer to send all relevant information to participants' usual sources of medical care. During your ARIC Study visit you indicated that we should send these results to you. We encourage you to share these results with your physician or usual source of medical care at the next convenient opportunity.

Our staff will continue to call you twice every year to stay in touch. Thank you again for being a member of the ARIC Study.

Sincerely,

_____

Principal Investigator

/xx

Attachment

Appendix 4: Template – CES-D Alert Letter (Visit 6)

Dear <**Name, provider of medical care**>

On <**Visit 6 exam date**> your patient, <**Name, ARIC Visit 6 participant**> participated in the 6th examination of the Atherosclerosis Risk in Communities (ARIC) Study. Depressive symptoms were assessed during this comprehensive exam, using the Center for Epidemiologic Studies Depression Scale (CES-D) Short Form.

As you know the CES-D is not a diagnostic tool but can 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.

Your patient had a CES-D score ≥ 9, suggesting probable Major Depression. At that time we recommended that your patient make an appointment with you for clinical follow-up and asked for authorization to contact you with this letter.

Please feel free to contact me if additional information is needed.

Sincerely,

<**ARIC Study Manager**>

c.c. <Name, ARIC Visit 6 participant>, <ARIC Principal Investigator>

Appendix 5.A: Results Letter Template – Typical

Dear [NAME]:

Thank you for taking part in the ARIC Study. The results for the tests you took related to memory and concentration are within the expected range for someone your age.

We are grateful for your time and effort as a member of ARIC.

Sincerely,

<signature>

<Name, date>

Appendix 5.B: Results Letter Template – Atypical

Dear [NAME]:

Thank you for taking part in the ARIC Study. The results of the tests you took related to memory and concentration are lower than expected for your age, and suggest that you may be experiencing some problems with memory or concentration. There are many possible conditions that may cause these difficulties, and our testing only represents results from one particular time.

Based on your test results, we recommend that you notify your personal physician or health care clinic to discuss whether you might benefit from further medical evaluation. We would be glad to assist with an appropriate referral if you do not have a personal physician or other source of health care.

We are grateful for your time and effort as a member of ARIC.

Sincerely,

<signature>

<Name, date>

Appendix 5.C: Results Letter Template – Undetermined

Dear [NAME]:

Thank you for taking part in the ARIC Study. Regrettably, because a limited number of measures could be completed during the exam, we are unable to provide an interpretation of the tests you took related to memory and concentration.

We are grateful for your time and effort as a member of ARIC.

Sincerely,

<signature>

<Name, date>