Manual 2

Field Center Procedures for Exam 4

Updated July 11, 2024

Version 2.1

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Manual Revisions

Version	Date	Revisions
2.0	June 15, 2023	▪ Removed COVID-19 screener from the reception section ▪ Updated exam components ▪ Removed sagittal abdominal diameter measurement ▪ Added diagrams for blood pressure measurement ▪ Added descriptions for ancillary study measurements (ankle-brachial index, neurocognitive assessment, pain/sensory, physical function, pulse wave velocity, Zio Patch) ▪ Added brief descriptions for questionnaires
2.1	July 11, 2024	▪ Refined summaries of questionnaires and scales ▪ Updated and included references for questionnaires and scales ▪ Removed death notification handout for internal communications ▪ Updated Table of Contents

MANUALS

Additional relevant manuals for Exam 4 include the following:

Manual 4: Blood Pressure

Manual 5: Electrocardiography

Manual 6: Echocardiogram

Manual 9: Specimen Collection and Processing

Manual 11: Data Management System

Manual 12: Quality Assurance and Quality Control

Manual 17a: MRI

Manual 17b: MRI Procedures

1 OVERVIEW

The Jackson Heart Study (JHS) is a longitudinal study designed to investigate the genetic and environmental risk factors associated with the disproportionate burden of cardiovascular disease among African Americans in Jackson, MS. The study recruited 5306 African-American adults living in the Jackson, MS metropolitan statistical area of Hinds, Madison, and Rankin Counties from 2000 to 2004. Participants were enrolled from 4 recruitment pools: participants enrolled in the Atherosclerosis Risk in Communities (ARIC) Study, 31%; volunteer, 30%; secondary family members, 22%; and random, 17%. Recruitment was limited to non- institutionalized adult African Americans 35-84 years old, except in a nested family cohort where those ≥21 years of age were also eligible.

JHS participants completed three consecutive clinic examinations in 2000-04 (Exam 1), 2005-08 (Exam 2), and 2009-13 (Exam 3). Exam 4, originally scheduled to start in March 2020, was delayed significantly because of the COVID-19 pandemic. The in-person Exam 4 started in July 2021, and was paused in November 2021. Exam 4 restarted in June 2022.

Manual 2 (Field Center Procedures for Exam 4) provides an overview of the interviews and clinical assessments conducted as part of Exam 4. This manual is one of a series of protocols and manuals of operation for the re-examination of the cohort. Additionally, because a number of procedures need to be described with full specifications, the following more detailed manuals of operation are available on the study website (except for ancillary study manuals).

Manual 4: Blood Pressure
Manual 5: Electrocardiography
Manual 6: Echocardiogram
Manual 9: Specimen Collection and Processing
Manual 11: Data Management System
Manual 12: Quality Assurance and Quality Control
Manual 17a: Magnetic Resonance Imaging (MRI)
Manual 17b: MRI Procedures
Manual 19: Pulse Wave Velocity (ancillary)
Manual 20: Atrial fibrillation (ancillary)
Manual 21: Physical Function (ancillary)
Manual 22: Ambulatory Blood Pressure Monitoring (ancillary)
Manual 23: Sensory/Pain (ancillary)
Manual 25: Resistant Hypertension (ancillary)
Manual 27: Stand-Up (ancillary)
Manual 28: 24-Hour Activity (ancillary)
Manual 29: Mindfulness (ancillary)

To ensure that all data collection is standardized and high quality, JHS personnel must be fully familiar with this manual of procedures and must be trained and certified in the procedures that they will be performing. The use of standardized data collection methods will allow for the investigation of patterns in the JHS data that reflect differences between study participants and changes over time, as opposed to differences between study technicians or deviations from the study protocol. Adherence to the study protocol is required for JHS to be able to meet its obligations to the study participants, to the scientific community, and to the funding agencies.

The main components of Exam 4 (in usual order of exam flow) are presented in **Table 1**.

Table 1

Exam 4 Components

Exam Component	
Reception and Informed consent Update demographic/contact/proxy/tracking information; complete reimbursement forms; complete participant safety form If cognitive difficulties suspected, administer six-item screener.	**Core**
Anthropometry Height, weight, waist/hip measures, and body composition	**Core**
Blood pressure	**Core**
Urine and blood specimen collection	**Core**
Snack	**-**
Neurocognitive Assessment Neurocognitive Test Battery** Ensuring Speech Understanding Mini-Mental State Exam (MMSE) Wide Range Achievement Test (WRAT 4) CERAD Immediate Recall Digit Symbol Substitution Test (DSST) CERAD Delayed Recall Incidental Learning Word Fluency (F, A, and S) Animal Naming Logical Memory I Digit Backwards Trail Making Test, Part A Trail Making Test, Part B Boston Naming Test Logical Memory II Clinical Dementia Rating Scale Neurologic History Depressive Symptoms	**Core and Ancillary**
Strength, balance, and movement assessment Chair stands Standing balance 4-meter walk	**Ancillary**

Exam Component	
Grip strength 2-minute walk test	
Echocardiography	**Core and Ancillary**
Edema Check	**Core and Ancillary**
Food Frequency	**Core**
Lunch	**-**
Electrocardiogram	**Core**
Pulse Wave Velocity	**Ancillary**
Ankle-Brachial Index	**Ancillary**
Zio Patch	**Ancillary**
Sensory (Pain) Assessment	**Ancillary**
General Interview Questionnaires Sociodemographic Psychosocial Food Security Global Chronic Stress Anger Expression Inventory Quality of Life Neighborhoods Sleep History Physical Activity Life Space Questionnaire Physical Ability Questionnaire Spirituality Questionnaire	**Core and Ancillary**
Medical Interview Questionnaires Medication Survey A Medication Survey B Personal Health History Women's Health History Respiratory Symptoms Diabetes Questionnaire Tobacco COVID-19 (waves 2 and 3 questionnaires) Community Assessment of Pain	**Core and Ancillary**
MRI Eligibility** Screening	**-**
Exit Interview	**-**
Brain MRI** (done on a separate day)	**Core**

Exam Component	
Ambulatory Blood Pressure Monitoring* ** (done on a separate day)	**Ancillary**
24-Hour Activity (ActiGraph, activPAL, GENEActiv devices) (done on a separate day)	**Ancillary**
Resistant Hypertension (24-hour urine collection) (done on a separate day)	**Ancillary**
Mindfulness (done on a separate day)	**Ancillary**
**Note: JHS-ARIC Shared participants will typically only complete the CERAD Word List Memory task (immediate and delayed recall) from the neurocognitive battery if the other measures were completed recently within ARIC. Also, JHS-ARIC Shared participants will not be offered the brain MRI screening or procedure if they completed the MRI in ARIC. ***JHS-ARIC Shared participants may be offered Ambulatory Blood Pressure Monitoring at the conclusion of ARIC Visit 10.	

A complete examination conducted at the JHS Field Center in the Jackson Medical Mall is the default, and is strongly preferred over other options. However, to accommodate a study participant's needs, Exam 4 may be split, abbreviated, or conducted at the participant's home as described below.

1.1 Split Exam

Exam 4 may be scheduled as a split exam (occurring across more than 1 study visit) if the study participant is unable to complete the full exam in a single setting. Split exams should be completed no more than 30 days apart. Under exceptional circumstances, the Field Center manager may authorize scheduling split examination beyond 30 days. Examples for when a split exam may be scheduled include:

- Adverse weather conditions;
- Absence of key personnel;
- Participant illness or fatigue;
- Participant is unable to complete exam during standard operating times.

An examination may be split if a medical alert condition requires that an exam visit be discontinued, and completion of the exam is scheduled once the condition prompting the alert is known to be resolved. Biospecimen collection may not be done more than once per participant. If an alert requires that the exam visit be stopped prior to the venipuncture, no biospecimen should be collected at that time, and the full examination is repeated at a later date. If an exam visit is discontinued after biospecimen was collected, this original venipuncture and specimen processing information is entered into REDCap and not repeated upon return of the participant. Blood pressure measurements are repeated (for safety reasons) at the return visit but the values are not recorded in REDCap. The intent is that the lab values and the blood pressure measurements in the JHS database correspond to the same time point.

On occasion, individual interview questions or exam components of a full examination may be missing, inadvertently or to accommodate various circumstances in the field. Completion of the missing component may be done while the participant is at the Research Exam Center or scheduled subsequently once flagged as missing in the data management report. Missing exam components must be completed within 60 days of the visit to maintain the temporal alignment in the baseline characterization.

When a study participant returns to the field center to complete an examination that was discontinued or split, they will be asked to initial and date the informed consent document that was signed during the first part of the examination to indicate consent for this portion of the examination.

1.2 Priority Components for Abbreviated Exam

Participants who are unable or unwilling to take part in a full examination may be offered an abbreviated examination that includes the priority components listed below in **Table 2**. As some participants may not consent to certain exam components (e.g., specimen collection), the Field Center manager may elect to proceed with questionnaires from the general interview or medical interview, if time permits, to allow for as much data collection as possible. Completion of the core exam components takes precedence over measurements conducted by ancillary studies.

Table 2

Priority Components for Abbreviated Exam

Abbreviated exam (2 ½ to 3 hours)
Consent
Anthropometry
Blood pressure
Urine and blood specimen collection
Echocardiogram ***OR*** Neurocognitive battery

1.3 Home Exam

Home visits (or visits to long-term care facilities) provide an opportunity to obtain important data on participants who may be frail, disabled, cognitively impaired, or serve as caretakers and are unable to come to the field center. With approval by the Principal Investigator, study participants who meet the above criteria may be offered an examination at their residence if they are located within a distance that allows for timely arrival and processing of biospecimen at the field center laboratory. If a home examination is required for a cohort member to take part in Exam 4 and processing of biospecimen within 120 minutes is not assured, a biospecimen collection at the field center should be attempted. The interview and examination procedures conducted at the home follow the study protocol as closely as the physical environment permits (**Table 3**). Two JHS certified staff attend each home visit to perform the study procedures and interviews.

Table 3

Priority Components for Home Exam

Home exam
Consent
Anthropometry
Blood pressure
Urine and blood specimen collection
Neurocognitive battery
Food frequency questionnaire
General interview questionnaires
Medical interview questionnaires

2 RECRUITMENT AND APPOINTMENT CONFIRMATION

The Exam 4 recruitment goal is to examine 2400 JHS participants. All surviving JHS participants are eligible to participate in Exam 4. Recruitment for Exam 4 will target participants who have expressed interest in Exam 4 (during their annual follow-up call or by calling study staff) and with targeted mailouts and phone calls based on their original enrollment month in the study. Recruitment postcards, brochures, and invitation letters will be mailed to participants and followed by recruitment calls to schedule Exam 4. Additionally, an invitation to schedule their Exam 4 appointment, as well as brief descriptions of components included in Exam 4, will be included in the study newsletter. Before calling a participant, study staff will have the available field center appointment dates/times, all relevant scripts, and copies of the recruitment materials. For tracking, the number of call attempts and their disposition (e.g., no answer, voicemail) should be recorded using the recruitment tracking and scheduling software.

After an appointment is scheduled, JHS staff make confirmation telephone calls to participants approximately one week and one day before their scheduled appointment. Confirmation of transportation will be made on the final reminder call.

2.1 Spousal pairs

For efficiency and to make the exam more convenient to participants, study staff will attempt to recruit spousal pairs at the same time, and to schedule their exams on the same day.

2.2 Legally authorized representative and proxy

JHS personnel are likely to interact and consult with individuals who serve as legally authorized representatives for a JHS cohort member or as proxies who contribute information additional to that

provided by a JHS participant. These contacts may happen during recruitment, the informed consent process, or in sharing information on a JHS 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 JHS participants, general guidance on the criteria by which the need to engage a legally authorized representative or proxy is determined, and describes their role in recruitment.

Federal regulations governing research involving human participants define a **legally authorized representative** as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participation in the procedure(s) involved in the research [45CFR46.102(c) and 21CFR50.3(l)]. In the state of Mississippi, the following individuals are considered Legally Authorized Representatives (in order):

- Health care agent
- Court-appointed guardian
- Spouse, unless legally separated
- Adult child
- Parent
- Adult brother or sister

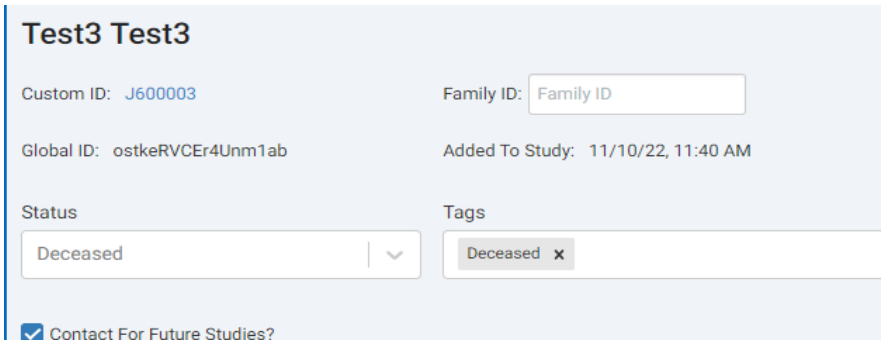
A **proxy or informant** is a person sufficiently familiar with the participant's daily activities to be able to provide information on the participant, such as answering questionnaires on behalf of the participant.

2.3 Participant Reported Deceased

During the Exam 4 recruitment or confirmation call, the staff member may be informed of the death of a participant. If so, staff will document this in the recruitment tracking and scheduling software using global tags and the assign task feature to notify other staff (**Figure 1**).

Figure 1

Tags for participant reported deceased



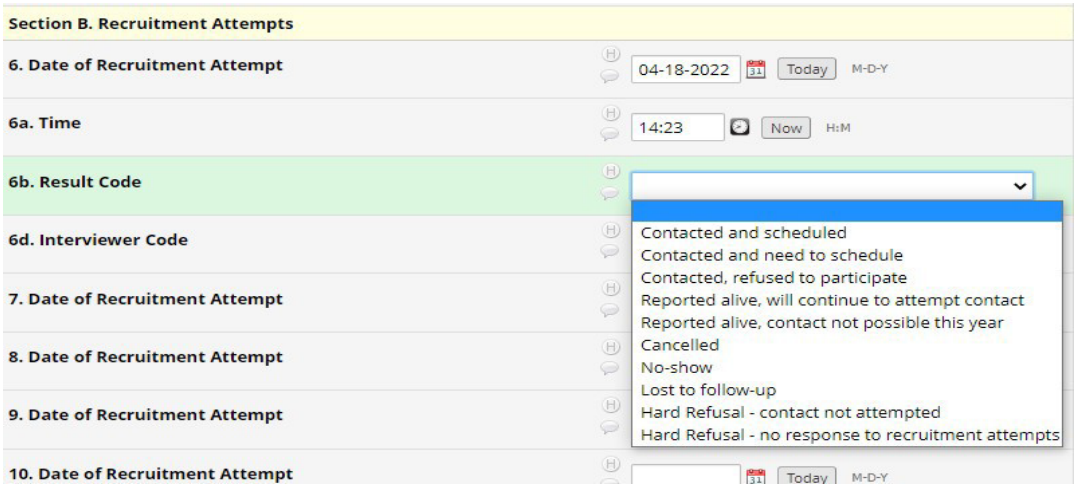
2.4 Participant Refusal to Participate

If at the time of the Exam 4 invitation call, the participant declines to participate in the exam, this information will be documented in the recruitment tracking and scheduling software.

If the participant expresses that they do not want to receive future contact from the JHS or to withdraw from the study, the specific request and notes from the communication will be documented and given to the Field Center Manager for final disposition (**Figure 2**).

Figure 2

Screenshot of Data Entry Options for Recruitment Attempts



2.5 Confirmation of Appointment

The instructions for the visit to the Field Center are specified in an information packet mailed to the participant two weeks before their scheduled exam date. The information packet includes:

1. Preparations:
   a) Instructions for fasting and proper hydration while fasting;
   b) Instructions concerning restrictions on the use of tobacco and vigorous physical activity the morning prior to the visit;
   c) Instructions on appropriate clothing to wear for the exam.
2. Items to bring to the field center:
   a) Medications and plastic bag for transporting them;
   b) Eyeglasses for reading;
   c) Hearing aids;

d) Name and address of health care provider(s) and/or clinic(s);
e) Name, address, email, and phone number of contact persons.

3. Logistics:
   a) Appointment date and time;
   b) Exam components and duration overview (optional);
   c) Reminder that snacks and lunch will be provided during the exam;
   d) Clinic hours and contact information for questions or rescheduling appointment;
   e) A map with directions to the field center location and parking facilities (or taxi arrangements, if applicable).

JHS staff will make reminder telephone calls to participants approximately one week and one day before their scheduled appointment. Confirmation of transportation will be made on the final reminder call.

3 RECEPTION

Each participant will be greeted upon arrival to the field center. If the participant appears to be ill, JHS staff will reschedule their appointment for a later date.

4 INFORMED CONSENT

The informed consent process is the first step in the course of the examination, and complies with federal regulations (45 CFR part 46) and institutional requirements by the University of Mississippi Medical Center. The primary objective of the informed consent process is to ensure the protection of the rights of JHS participants, inform participants about the study components, meet federal regulations and institutional requirements, and to identify and document the participant's decisions for completing various study components. The informed consent process reviews the study participant's right to withdraw from the study, to not participate in a study component, or to decline to answer questions without penalty.

4.1 Administration to Participant

Informed consent for participation in Exam 4 is obtained before administering any interviews or procedures. Time is allowed for the participant to read and ask questions about the informed consent document in a private area. If the participant is visually impaired or otherwise unable to read the document, the narrative portion is read to them and then the participant is asked whether they have questions. At all times, questions are encouraged, and ample time is allowed for the person to read and sign the informed consent document. The original informed consent document is filed in the participant's Exam 4 chart and uploaded to the network drive. A copy of the informed consent document is also given to the participant.

Staff certification requires demonstration of adequate technique on 5 informed consent administrations. Certifications are reviewed and maintained by the Field Center manager, and the list of staff certified to consent study participants is on file with the study's approved IRB protocol.

4.2 Ability to Comprehend the Informed Consent

Although the capacity to provide informed consent is required for the JHS 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, the JHS 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 or 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"). An individual who seems to always be looking to their spouse or a companion for answers to historical questions or medical history questions may also warrant consideration for potential cognitive impairment.

To ensure that participants understand the informed consent process and document, staff can ask the participant to explain back certain portions in their own words. This can be introduced by stating that it is very important that the participant understand their rights and the process by which the study protects the confidentiality of the participant's information. If the responses from the participant suggest that they have difficulty comprehending the consent process or the document contents, the staff person brings this to the attention of the Field Center manager. The participant's performance on the six-item cognitive screener (i.e., unable to repeat the three questions presented as part to the introduction to the six-item screener, fails the three orientation questions, or scores at 2 or below on this screener) will guide staff in determining whether to recruit a Legally Authorized Representative.

4.3 Informed Consent by Legally Authorized Representative

Cognitive deficits may affect the ability to provide informed consent and to accurately respond to interviews and questionnaires. Procedures are implemented to identify participants: (1) considered vulnerable due to diminished cognitive functioning, 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 Legally Authorized Representative to participate in the JHS. In addition, access to a knowledgeable alternate respondent who can assist with interviews and questionnaires is requested for participants falling into the second category, where self-report may be suspect. Staff should encourage the participant to respond to the questionnaire items unless the

participant is unable to do so. JHS participants who take part in Exam 4 under a consent by Legally Authorized Representative are offered all study procedures that are not preempted by a safety exclusion, and interviews.

It is important to identify the need for a Legally Authorized Representative prior to Exam 4, if possible, so that the participation of that individual can be scheduled and confirmed. If the need for a Legally Authorized Representative becomes apparent only at the time of Exam 4, the visit must be discontinued until informed consent by a Legally Authorized Representative has been obtained. The disposition of data collected during the exam on a participant subsequently deemed to require a Legally Authorized Representative should be guided by consultation with the local IRB and the JHS Principal Investigator.

5 FIELD CENTER EXAMINATION PROCEDURES AND INTERVIEWS

5.1 Overview

The components of Exam 4 are listed in **Table 1**. Study participants are asked to fast for at least 8 hours and to abstain from caffeinated beverages and from smoking on the morning of their examination. Following informed consent, a first set of procedures and examinations is conducted in the fasting state, prior to the participant receiving a morning snack. With the exception of informed consent, the procedures performed in the fasting state can be administered in any sequence while the participant is fasting. The average duration of Exam 4 is 5 to 6 hours.

5.2 Participant Safety Screening

The Participant Safety Screening Form (PSA) is used to screen a participant for special needs and to ensure their safety for the exam components. The conditions reviewed include the participant's use of a pacemaker, defibrillator or other implanted electronic device, mobility issues, and diabetes status. The responses are recorded on the PSA form, the participant is informed of any procedures that they are ineligible for, and the excluded procedures are recorded on the participant exam checklist.

5.3 Scheduling the Participant's Medications on the Day of the Exam

Arrangements are made for the participant to have access to their medication that needs to be taken during the course of the exam at scheduled times, and with food if required. Participants who have conditions that require the use of medication are instructed to do the following:

- Antihypertensive medications should be taken according to the participant's usual schedule for these medications. This is recommended to avoid changes in a participant's usual blood pressure on the day of the exam, and in order to avoid abrupt changes in blood pressure and possible hemodynamic events.
- Anti-anginal medication such as nitrates 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.
- Participants who have diabetes and take *oral hypoglycemic medications* can withhold taking them until the blood draw and their snack.
- Participants who have diabetes and take *insulin* should be asked to withhold the morning dose until the blood draw and snack. These participants will be reminded to bring their insulin to the field center on the day of their exam, and the staff will arrange for the safe storage of their medication until it is time for them to administer their insulin dose after the snack. Participants who use insulin will also be advised to check their capillary glucose level two hours after the snack.
- Other medications 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.

6 ANTHROPOMETRY

Anthropometric measures include height, weight, waist circumference, hip circumference, and body composition (body fat and fat mass).

6.1 Equipment and Supplies

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

- Tanita Body Composition Analyzer, model TBF-400
- Befour Professional Healthcare Scale, model MX450
- Wall mounted stadiometer
- Gulick II 150 and 250 cm anthropometric tapes
- Full length mirror
- Calibration weights (10 kg)

6.2 Data Collection

It is preferable to have 2 trained staff (an examiner and a recorder) for each measurement. The examiner is responsible for positioning the participant, taking each measurement, and calling the measurement aloud to the recorder. The recorder writes the recorded measurements on the checklist, keys the information into REDCap, and asks the examiner to confirm or re-measure any out-of-range measurements identified by the data management 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 REDCap. Measurements are recorded in metric units and entered into the Anthropometry (ANT) form, except for arm circumference which is entered into the Sitting Blood Pressure (SBP) form. If applicable for those unable to stand unassisted, self-reported height is recorded in feet and inches and self-reported weight is recorded in pounds.

6.3 Examination Procedures

For all measurements, participants should wear scrub suits or light, non-constricting clothing and slippers or socks. When measuring weight and body composition with the Tanita scale, participants must be barefoot.

6.3.1 Standing Height

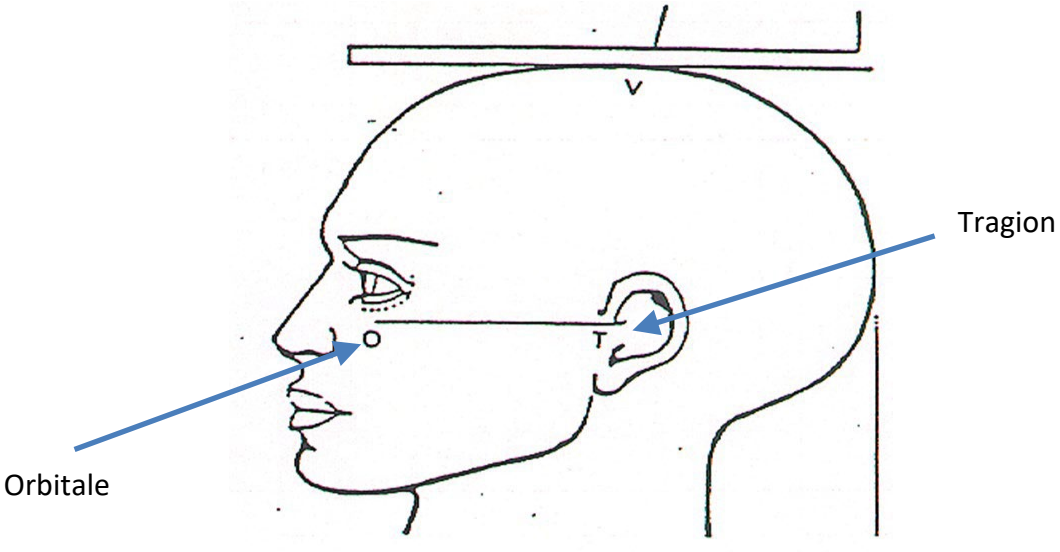
If the participant cannot stand on both feet unassisted, ask the participant their height (in feet and inches) and record it on the self-reported height of the ANT form, rounding to nearest inch.

The participant stands erect on the floor or the horizontal platform with their back against the vertical metal centimeter ruler mounted on the wall. The heels are placed together and positioned against the vertical ruler. The participant is instructed to stand as straight as possible, with feet flat on the floor. The participant looks straight ahead with their head in the Frankfort horizontal plane (i.e., the horizontal plane that includes the lower margin of the bony orbit, the bony socket containing the eye and the most forward point in the supratragal notch, the notch just above the anterior cartilaginous projection of the external ear) (**Figure 3**). The right angle is brought down snugly, but not tightly, on the top of the head.

Allowance should be made for high hair styles and head coverings. If possible, request the participant to remove the head covering or loosen the hairstyle. A footstool is used if the examiner is shorter than the participant such that the examiner's view is level with the point of measurement on the head of the participant. The participant's height is recorded in centimeters, rounding to the nearest decimal point.

Figure 3

Frankfort Horizontal Plane for Measuring Height



Frankfort horizontal plane: orbitale-tragion line horizontal
Orbitale: Lower margin of eye socket
Tragion: Notch above tragus of ear or at upper margin of zygomatic bone at that point

6.3.2 Weight and Body Composition

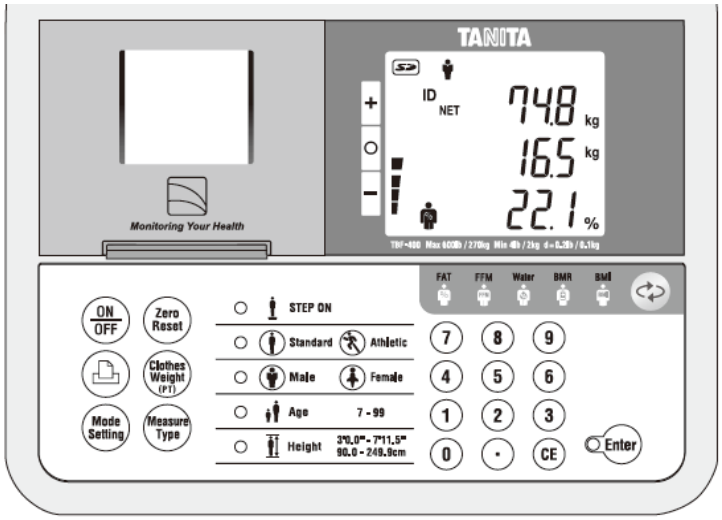
If the participant cannot stand on both feet unassisted, ask the participant their weight and record it on the self-reported weight section of the ANT form, rounding to the nearest pound. Use Befour (wheelchair) scale to measure the participant's weight. No data on weight or body composition will be collected using the Tanita scale.

For participants who are able to stand, as an important safety precaution, before taking any measurement on the Tanita scale, ask the participant whether they have a pacemaker or defibrillator, an artificial joint, a metal plate, rod, or other metal in the body. If the answer is yes, use Befour scale to measure participant's weight. No data on weight or body composition will be collected using the Tanita scale.

If the participant does not have any safety exclusions, proceed with Tanita scale measurements. The control panel of the Tanita scale is depicted in **Figure 4**. 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 4

Control Panel of the Tanita Scale



Meanings of the LED Indicators and Keys

ON OFF	Turn ON / OFF the power
	Feeds the printer paper
Mode Setting	Set various functions
Zero Reset	Reset zero point
Clothes Weight (PT)	Set preset value (Clothes weight)
Measure Type	Select measurement mode
	Select measurement display

FAT	Display Body Fat (percentage and mass)		
FFM	Display Fat Free Mass (percentage and mass)		
Water	Display Body Water (percentage and mass)		
BMR	Display Basal Metabolic Rate	BMI	Display Body Mass Index

STEP ON	Indicate to step on
Standard / Athletic	Select the body type from "Standard mode" or "Athletic mode"
Male / Female	Select the gender from "Male" or "Female"
Age 7 - 99	Enter the age between "7 to 99 years"
Height	Enter the height between "3'0.0" to 7'11.5"/90.0 to 249.9cm"
Enter	Confirms the entered numerical value.

1. Initial set-up.

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

2. Setting the number of print outs and printing language.

   Turn the unit on by pressing the ON/OFF key. If there is no printer paper in the feeder, "P- End" will flash on the LCD. If you DO NOT want to use printer paper, press the [CE] key to continue measurement with no printer paper. When there is no "P-End" message, but the printer fails to print, the chosen number of print outs may be "0". Select a number of printouts greater than "0".

- Set the number of printouts and the 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. Using the number keys, enter '3' to obtain 3 printouts (one for participant, one for provider, one to be filed in participant chart). The LCD will then automatically advance to language selection. Select [1] for English. When input has been completed, the unit will automatically switch to the measurement section. If further changes are needed, turn off the unit, and repeat the steps for setting number of printouts and language.

3. Once all presets have been completed, after a momentary delay, the ◄ mark and "0.0" will appear on the LCD. If measuring units need to be changed, do so at this time by pressing the [kg/lb] key. An arrow on the LCD will follow the selection of weighing units. Throughout the data entry, mistakes may be corrected by pressing the [CE] key. Follow the flashing arrow on the LCD for proper sequence.

   The following additional steps must be completed <u>BEFORE</u> the participant steps on the scale:

- Enter the Clothes Weight. ENTER "0.0". In order to allow comparability between the weights obtained via the Befour scale and the Tanita, no allowance will be made for clothes weight.
- Enter Gender and Body Type. Select from one of the four body types: Standard Male, Standard Female, Athletic Male, or Athletic Female. For most participants, you will select the "Standard" mode. The Athletic key should be used for individuals under the following conditions:

  Tanita defines "athlete" as a person involved in intense physical activity of at least 10 hours per week and who has a resting heart rate of approximately 60 beats per minute or less. Tanita's athlete definition includes "lifetime of fitness" individuals who have been fit for years but exercise less than 10 hours per week. Tanita's athlete definition does not include "enthusiastic beginners" who are making a real commitment to exercising at least 10 hours per week but whose bodies have not yet changed to the required Athlete mode.

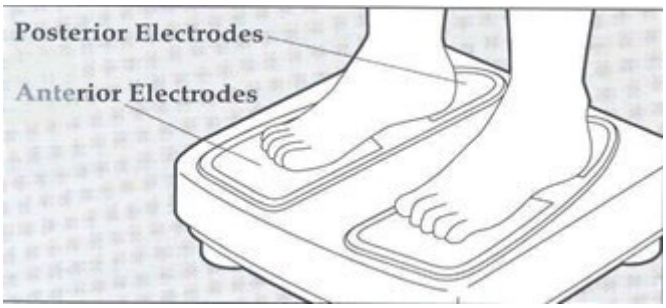
- Enter Age. Enter age using two digits.

- Enter Height. Using the nearest 0.5 decimal point, enter the height obtained from either the wall mounted metal ruler or, if doing an offsite examination, the height obtained from the Tanita height ruler. Height will automatically be rounded up or down to the nearest 0.5 or whole number.
- Set the Target % body fat. Acceptable levels of body fat range between 18-25% for men and between 25-31% for women. Explain to the participant that you are selecting the mid/upper level of the acceptable range by entering 24% for men and 30% for women. You may also inform them that the "fitness" levels are between 14-17% for men and 21- 24% for women, and that the "essential" fat that is necessary is 2-4% for men and 10- 12% for women.

Check the participant's feet for calluses. If the participant has thick calluses on their feet, place 0.5 cc of a conductant (saline, water) in the center of each electrode. After assuring that the participant's feet are clean (have them use a wipe to cleanse the bottom of their feet), ask the participant to step onto the scale when the flashing arrow appears next to STEP ON and the LCD screen displays "88888." Instruct the participant to make sure the heels are placed on the posterior electrodes and the front part of the feet is in contact with the anterior electrodes as indicated in **Figure 5**. The weight will be displayed on the upper portion of the LCD screen.

Figure 5

Foot Placement for Body Composition Measurement

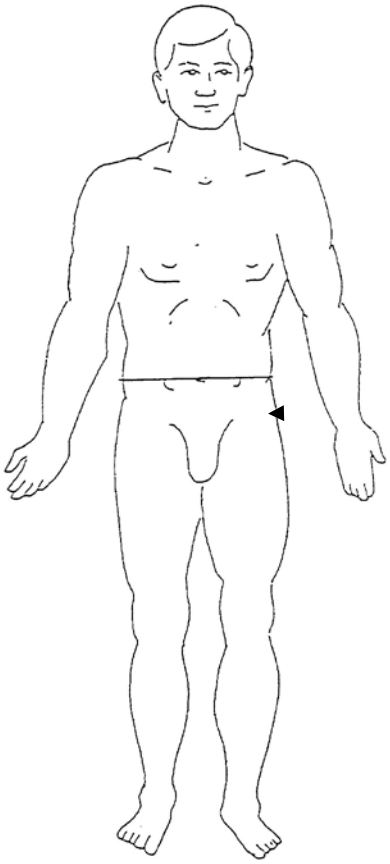


6.3.3 Waist Girth

The participant is instructed to stand erect and relaxed with the feet approximately 6 inches apart and the weight equally distributed on both feet. The participant is asked to lift their top just high enough to make the area visible (hands must not go above waist level). An anthropometric tape is applied at the level of the umbilicus (navel) and the participant is instructed to breathe quietly. The tape should be snug, but not so tight as to compress tissue (**Figure 6**). The full-length mirror or a 2nd staff member verifies that the participant is standing erect and that the tape is horizontal. The measurement is recorded in centimeters, rounding to the nearest decimal point, at the point of relaxation end exhalation.

Figure 6

Location of Waist Girth Measurement

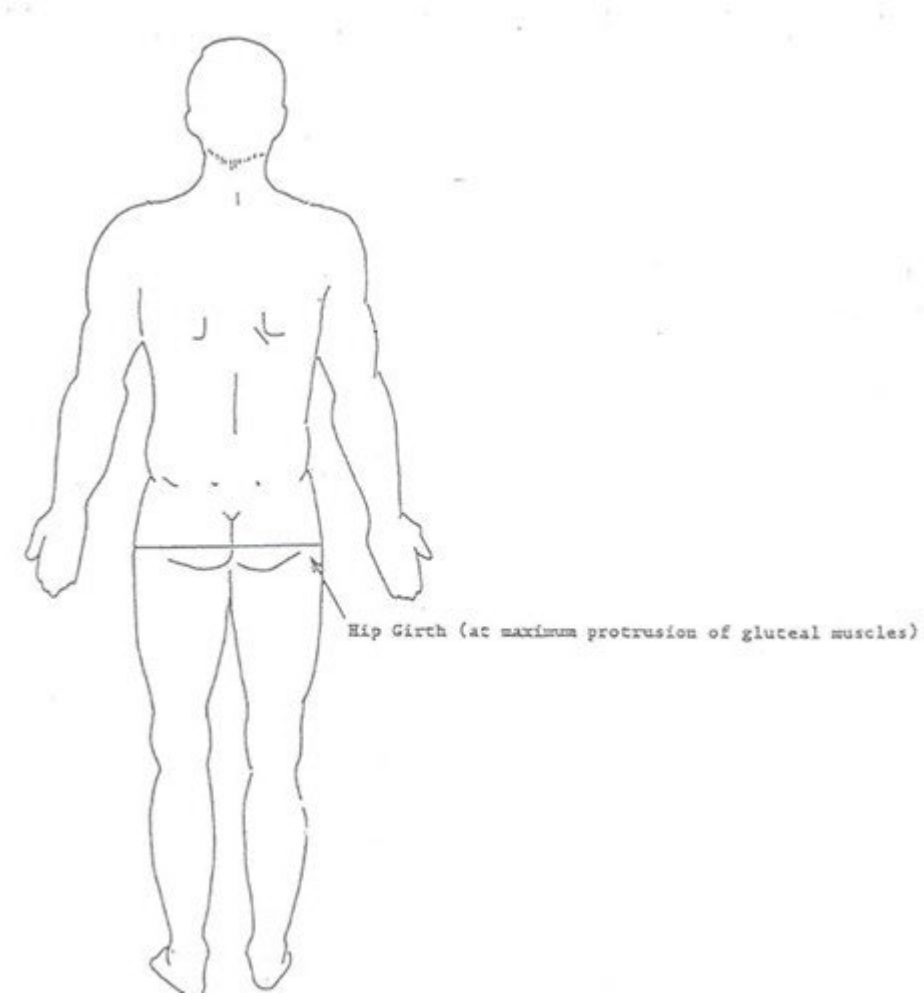


6.3.4 Hip Girth

The participant stands erect, yet relaxed, with weight distributed equally over both feet and with the feet together. The hip girth is measured at the level of the maximal protrusion of the gluteal muscles (hips) (**Figure 7**). The tape is placed horizontally around the participant's gluteal muscles (hips) at the level of maximal protrusion. The position is verified by passing the tape measure above and below the observed maximum. The tape is kept horizontal at this level and the measurement is recorded in centimeters, rounding to the nearest decimal point.

The most common source of error for this measurement is due to not having the tape horizontal and not verifying that the maximum width is being measured. The position of the tape is checked from both the front and the back.

Figure 7
Location of Hip Girth Measurements



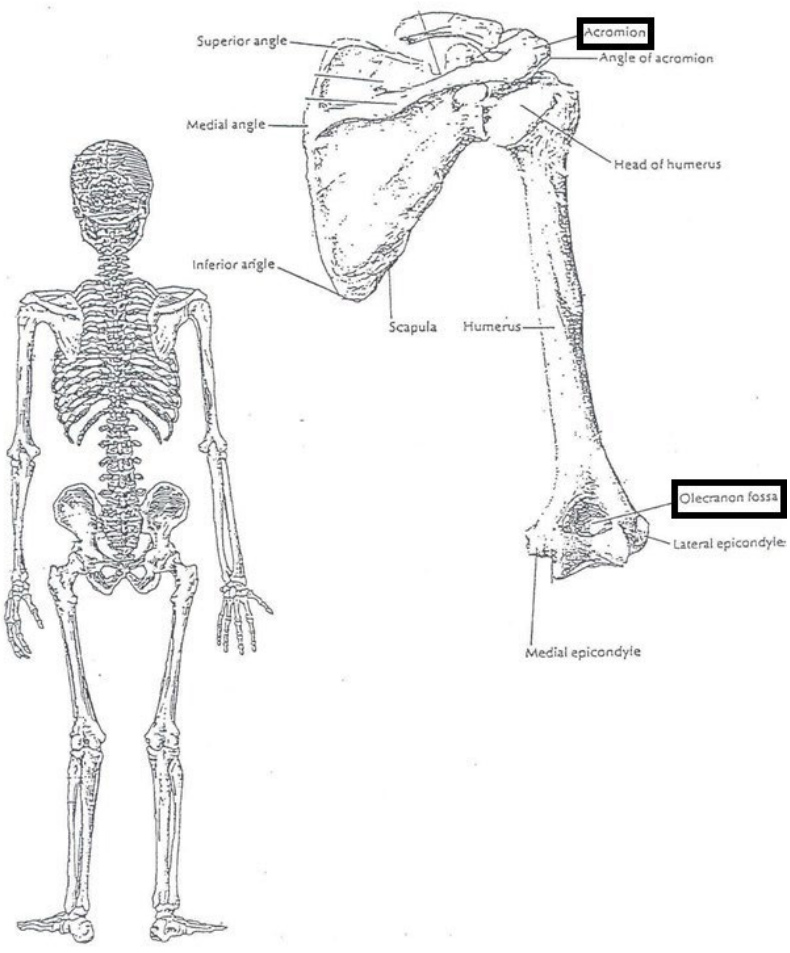
6.3.5 Arm Circumference

The participant stands facing away from the staff member with the right arm flexed at 90 degrees at the elbow, hand across midsection. The observer determines and marks the tip of the olecranon (elbow). Bony landmarks for measuring the circumference of the right arm are depicted in **Figure 8**. The participant straightens the arm, allowing it to hang loosely at the side. The staff then determines and marks the posterior tip of the acromion process (shoulder bone). Using a centimeter tape, the staff measures the length of the upper arm between the two marks and marks the midpoint.

The staff wraps the tape around the arm at the midpoint mark, making sure that the tape is level. The arm circumference is measured in centimeters, rounding to the nearest decimal point, and is recorded on the Sitting Blood Pressure (SBP) form.

Figure 8

Bony Landmarks for Anthropometric Measures



6.3.6 Body Fat Percentage and Fat Mass

Body fat percentage and fat mass are automatically measured once the weight measurement has stabilized on the Tanita TBF-400 Body Composition Analyzer scale. The participant continues to stand with their heels and front parts of the feet in contact with the posterior and anterior electrodes of the scale unit as described above (**Section 6.3.2**). After the weight stabilizes, the impedance measurement is taken. This is denoted by four "bubbles" ▫▫▫▫, which appear on the bottom half of

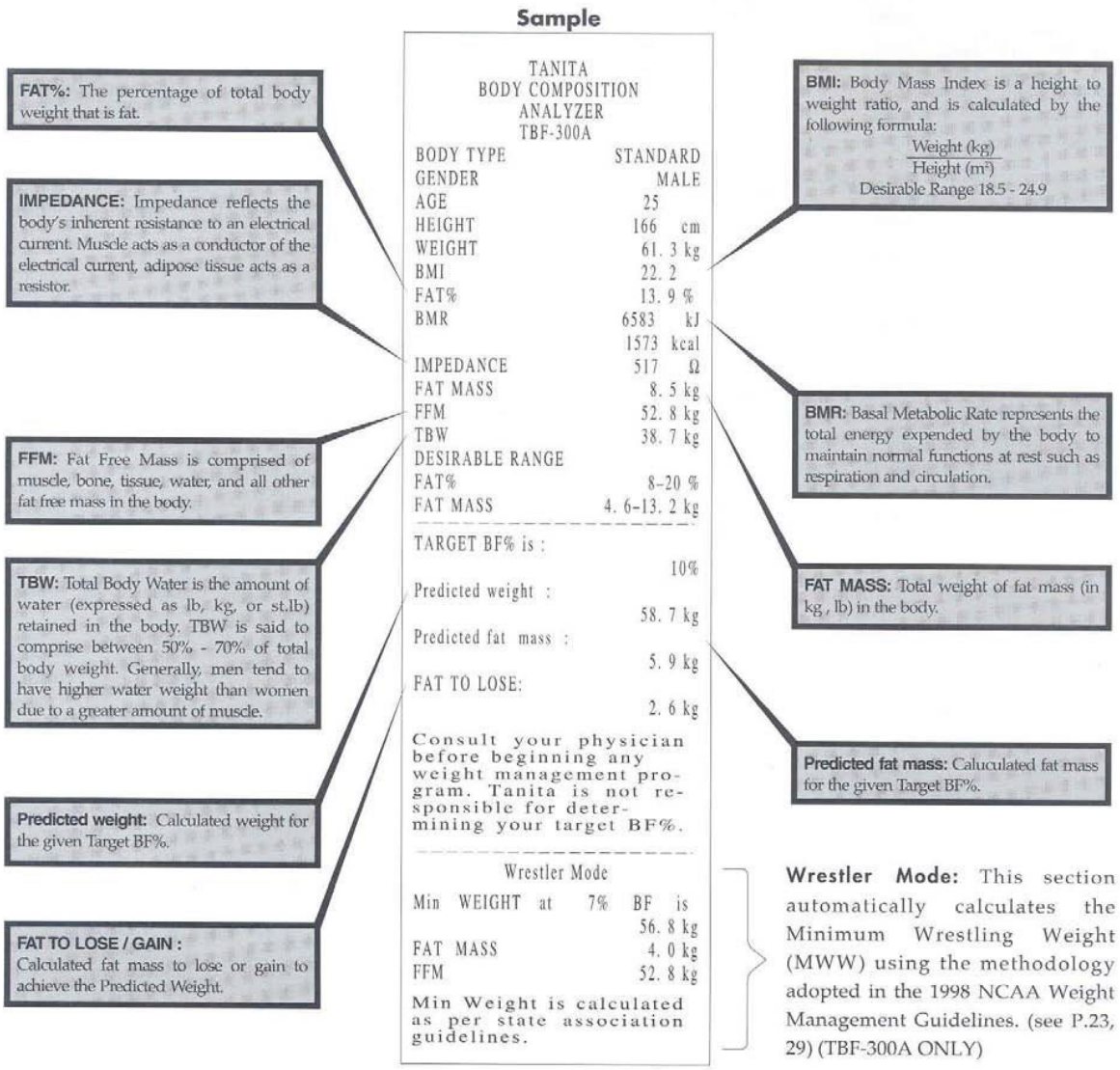
the LCD. As the measurement is being made, each of the bubbles will disappear one by one. It is important that the participant not step off the scale until the last bubble has disappeared and the display emits a short BEEP.

When measurement is complete, both weight and percent body fat will be displayed on the LCD, and detailed results will automatically print out. The LCD will then return to the Gender and Body Type screen in about 10 seconds, making it ready for the next participant.

Figure 9 shows an example printout with explanations. Fat%, impedance, fat mass, lean body mass (FFM), and total body water (TBW) measures are recorded from the printout onto the Anthropometry (ANT) form.

Figure 9

Sample Tanita TBF 300A Body Composition



6.4 Quality Assurance

6.4.1 Training and Certification

Staff training includes (1) an introduction to the rationale for body size measurements, the expected limits of reproducibility, and usual errors; (2) a demonstration of proper and improper procedures; (3) practice on volunteers; and (4) testing on volunteers with four different body types—lean, obese, athletic and aged.

Criteria used for initial certification and recertification for anthropometry and body composition determination is outlined in the Quality Assurance and Quality Control manual (Manual 12) and includes the following criteria:

- The standing height measurement must agree within 0.25 cm of the trainer/certifier.
- The waist/hip circumference measurements must agree within 2.2 cm of the trainer/certifier.
- Weight must agree within 0.2 kg of the trainer/certifier.
- Recertification is performed every 6 months. The following additional certification criteria for each type of measurement used must be met:
    - Absence of digit preference for more than 6 months during one year;
    - Absence of systematic differences in mean values;
    - Adequate performance on replicate measurements;
    - Quarterly quality control observations of technicians by an observer are also performed and documented on the Summary of Observation and Equipment Checklists (see Appendix 1).

6.4.2 Equipment Calibration

To maintain accuracy, the scale is zero balanced daily and calibrated with a known weight (10 kg) every week or whenever the scale is moved. The scale is professionally calibrated and serviced annually.

The height ruler is observed weekly to see that it (a) touches the hard-surfaced floor or platform on which measurements are done, and (b) is perpendicular to the floor. This weekly check is recorded on the Anthropometry Equipment Calibration Log (see Appendix 2).

The tapes used for measuring girth are calibrated monthly against the metal height rule. Tapes that show damage or wear or that do not measure within the required range are replaced.

Equipment calibrations are documented on the Anthropometry Equipment Calibration Log and summarized on the Summary of Observation and Equipment Checklists (see Appendix 1).

6.4.3 Quality Assurance Monitoring

The Summary of Observation and Equipment Checklist is sent to the Coordinating Center and reviewed quarterly. Digit preference, systematic differences in location statistics and random repeat observations are analyzed and reviewed monthly by the Quality Control subcommittee.

7 SITTING BLOOD PRESSURE

Sitting blood pressure is measured using the Omron HEM-907XL blood pressure monitor (**Figure 10)** and the results are recorded on the Sitting Blood Pressure (SBP) form. Sitting blood pressure protocol and procedures are detailed in **Manual 4 Blood Pressure**.

7.1 Equipment and Supplies

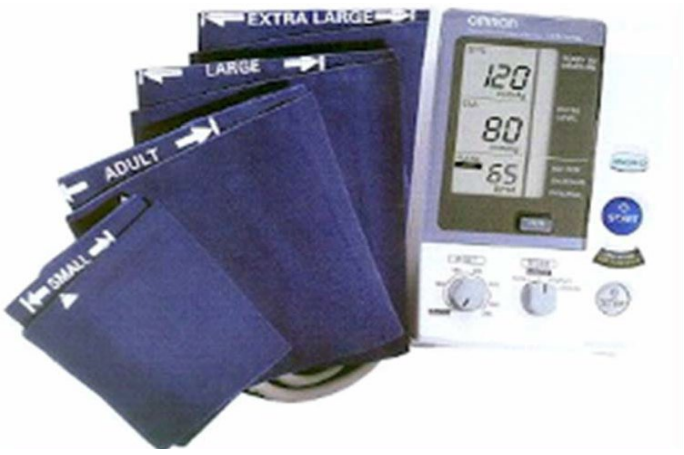
Equipment	Supplies
Omron HEM-907XL	Antibacterial wipes
4 cuff sizes	Alcohol wipes
Tape measure	Tissue
Foot stool	Gauze
Timer	Water soluble ink pens

7.2 Sitting Blood Pressure (SBP) Form

The SBP form is used to record arm measurements used to guide blood pressure cuff size selection and serial measurements of both blood pressure and pulse rate.

Figure 10

Omron HEM-907XL Blood Pressure Monitor



7.3 Examination Procedures

The staff greets the participant and explains that their 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 participant observes their 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 staff asks if the participant has questions before proceeding.

7.3.1 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 participant self- reports 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 (item 1). Measurements are not done on any arm that has rashes, small gauze/adhesive dressings, casts, is withered, puffy, has tubes, open sores, hematomas, wounds, arteriovenous (AV) shunt, or any other intravenous access device. Also, participants 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 and this will be noted in the comments section of the SBP form.

7.3.2 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).

Measurement of Arm Circumference

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

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 2**. For 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 (item 3).

Table 2

Arm Circumference and Corresponding Cuff Size

Arm Circumference (cm)	**Cuff Size**
17.0 to 21.9	Small (17-21.9 cm, HEM-907-CS19)
22.0 to 32.5	Adult (22-32.5 cm, HEM-907-CR19)
32.6 to 42.5	Large (32.6-42.5 cm, HEM-907-CL19)
42.6 to 50.0+	X Large (42.6-50+ cm, HEM-907-CX19)

Special Situations

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 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.*

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 a large arm, which can lead to misclassification of an individual as hypertensive. *Record the use of the R/L forearm in item 1 of the SBP form and add a note log to this effect.*

7.3.3 Positioning the Participant and Placing the Cuff

Ask the participant to sit and rest quietly in the chair, adjusting it, if necessary, to allow the participant's feet to rest flat on the floor. 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 bare 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.

Locating the Pulse Points

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 biceps muscle and slightly towards the body. For brachial artery palpitation, fingertips or thumb may be used (**Figure 11**).

Figure 11

Locating the brachial pulse

Placing the Cuff

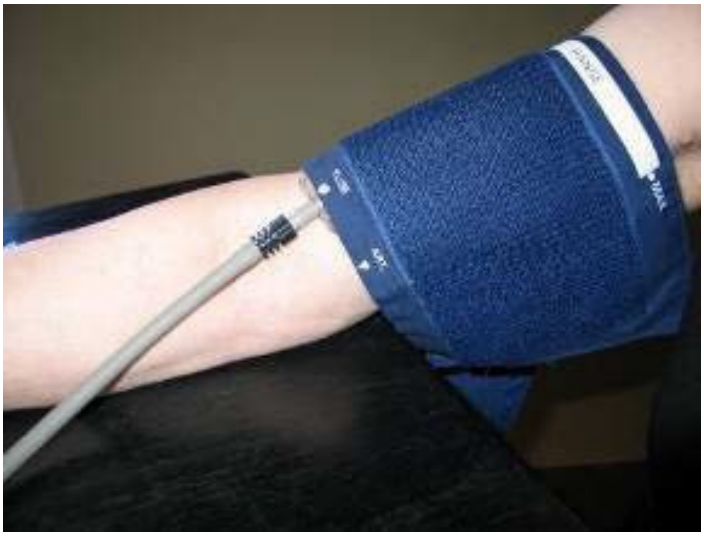
Wrapping the blood pressure cuff around the arm. The cuff should be wrapped in a circular manner. Do not wrap the cuff in a spiral direction. Check the fit of the cuff to ensure that it is secure but not tight.

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 (**Figure 12**).

For short or large 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 (item 3).

Figure 12

Placing the Cuff



7.3.4 Procedures for the Omron HEM-907XL

Omron HEM-907XL Set-up

At the start of each session check that the monitor is attached to the AC adapter to the DC jack and plugged in (**Figure 13**) and AC sign (**Figure 14**) is visible in the lower window.

Figure 13

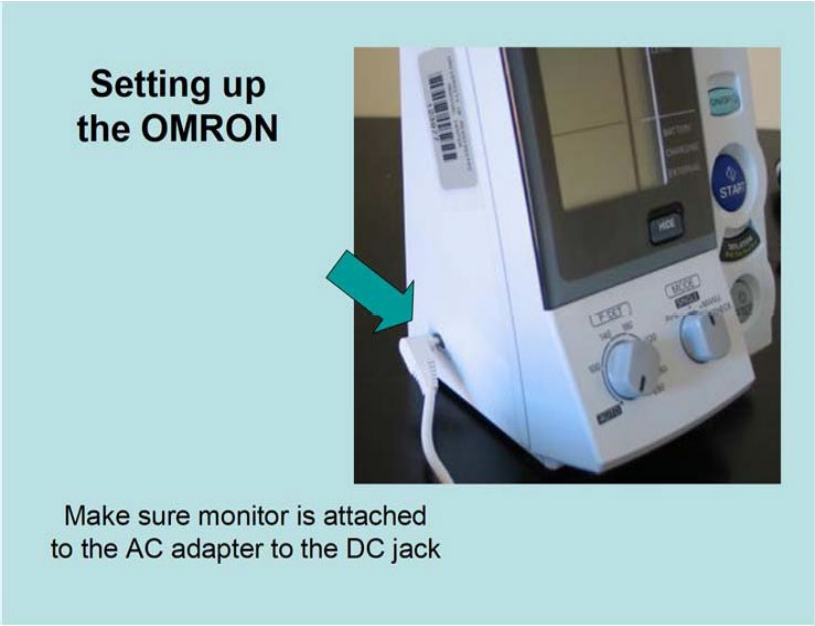


Figure 14

Setting up the OMRON

When the power is OFF, push the ON/OFF (power) button for more than three seconds while holding the START button simultaneously: F1 is displayed in the first window and three inflation (3) is displayed in the middle window (**Figure 15**). If needed push the DEFLATION (deflation control)/Measurement Result Display Switch Button to change the set value to 3 inflations.

Figure 15

Powering on the OMRON

Push the START button and F2 function is displayed in the first window and 0 waiting time is displayed in the middle window (**Figure 16**). If needed push the DEFLATION (deflation control)/Measurement Result Display Switch Button and change the set value to 0 sec waiting time.

Figure 16

Starting the OMRON

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

Figure 17

OMRON Display

Table 3 summarizes the settings for the exam.

Table 3

Settings for Omron HEM-907XL

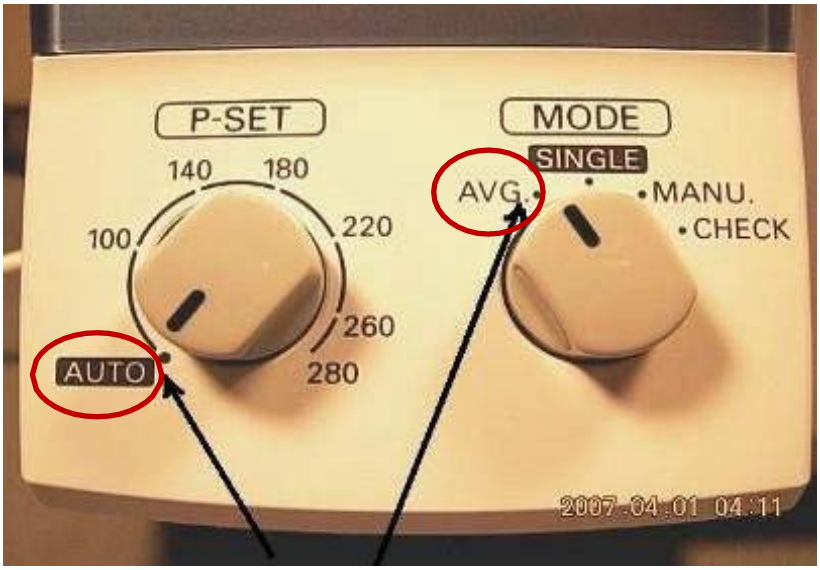
Function #	Items to set	Set value
F1	Number of inflations	3 times
F2	Waiting time to start the first inflation	0 sec
F3	Inflation interval	30 sec

Measuring Blood Pressure

Once these settings are validated, the measurements 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 18**).

Figure 18

Measuring Blood Pressure



Next, connect the air tube to the cuff. 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 the Omron unit. Wrap and secure the appropriate cuff to the participant's upper right arm**.**

Figure 19

OMRON Start Button

Record the time of blood pressure measurement in the SBP form (item 4), then push the START button to start the measurements (**Figure 19**). 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 20**).

Figure 20

Dial Display

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 hands as in **Figure 21** 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 21

Participant Gestures

<u>Recording the Omron Results</u>

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 14-16. Push the DEFLATION button to toggle to the first set of measures and record the 1st set on the SBP form in items 5-7. 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 8-10 and 11-13, 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 Field Center manager on site before participant leaves the field center. The study nurse should evaluate the possible reasons for an abnormally high or low heart rate and consult with the Cardiologist on call to 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 protocol be repeated. An evaluation performed by a clinician may include a seated blood pressure, which is not recorded on the SBP form.

Push the ON/OFF button. This ends the blood pressure measurements for the participant.

7.4 Reporting Blood Pressure Values

The participant's blood pressure values are not discussed at the blood pressure station nor during the measurement process. The staff 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 staff can add that the research protocol requires that results not be discussed during the exam. 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 exam and also as part of the consolidated report of study results that the field center sends to the study participant (and their health care provider, if instructed by the participant). In each case, the average systolic and diastolic pressure values recorded on the form are retrieved from REDCap 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 JHS staff explain the recommended follow-up for the pertinent blood pressure level according to the 2017 Evidence-Based Guideline for the Management of High Blood Pressure in Adults.

As a participant safety procedure, if the average blood pressure is ≥180 mm Hg systolic or ≥120 mm Hg diastolic, the staff 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 11**, and repeats the blood pressure measurement steps. This second set of blood pressure values is recorded on the SBP form and entered into REDCap instead of the first set.

If the average blood pressure of the second set of readings is ≥200 mm Hg systolic or ≥120 mm Hg diastolic, the staff 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 Field Center manager, JHS staff then assist the participant in scheduling a same-day visit to their health care provider, or arranges transportation to the nearest emergency room for a medical evaluation of the participant's blood pressure. If the average blood pressure of the second set of readings is 180-199 mm Hg systolic or 110-119 mm Hg diastolic, the field center examination may proceed, and JHS staff assists the participant in scheduling an appointment with a medical professional within 48 hours, to determine whether treatment should be started or changed.

7.5 Equipment Maintenance

Staff will maintain all blood pressure equipment used in the field center. The steps that staff follow to check and maintain equipment include the following:

- 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.

8 COGNITIVE TESTING

To identify and characterize dementia and mild cognitive impairment (MCI) in the JHS cohort, an efficient but comprehensive neuropsychological assessment will be administered by trained and certified staff. 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 implemented in 2005 across all National Institute on Aging-sponsored Alzheimer's Disease Centers.

The neurocognitive assessment has 2 stages. Stage 1 includes the full cognitive test battery administered at Exam 4. The neurocognitive battery is designed to assess multiple domains including: global mental status, memory, language, and executive function/processing speed, and olfaction. Test scores are compared to age, education, and race-specific normative data to identify those with suspected dementia or MCI. Stage 2 consists of informant interviews and is limited to participants who are selected based on cognitive performance. Stage 2 is conducted at Exam 4 if a proxy is present or by telephone shortly after the exam. The Stage 2 informant interviews must be conducted within 3 months of the exam visit.

8.1 Stage 1 (In-Person Neurocognitive Assessment)

The neurocognitive test battery takes about one hour, depending on the cognitive ability of the participant and is preferably administered at the beginning of the exam visit after the blood collection and processing and the participant has had a snack. It is not ideal to conduct the cognitive testing on participants in a fasting state because food- and beverage-deprived participants may be less motivated to cooperate and less likely to perform their best.
Neurocognitive testing should not be conducted after 2pm in the afternoon.

The order of administration for the cognitive testing is listed in **Table 4**. Trained and certified staff will administer the cognitive function tests in this fixed order, one right after the other, during a single session in a quiet room. Study examiners must follow a standardized procedure to ensure reliable and valid data.

Tests are administered following the instructions printed on the Neurocognitive Test Battery Packet and QxQ instructions. Responses are recorded on the paper test packet by the examiner

or by the participant and kept in the participant's folder. Tests are scored and test results are tabulated by the certified and trained staff only after the participant has completed the tests and has left the room. Test results are summarized on the Neurocognitive Summary Score (NCS) form and keyed into REDCap by staff immediately following the testing session.

Table 4

Order of Administration of Neurocognitive Tests

Test	Form Code
Block A	
Ensuring Speech Understanding	ESU
Mini-mental State Examination Test	MME
Wide Range Achievement Test (WRAT)	NCS
CERAD Immediate Recall*	NCS
Digit Symbol Substitution Test (DSST)	NCS
CERAD Delayed Recall*	NCS
Incidental Learning	NCS
Word Fluency (F, A, and S)	NCS
Animal Naming	NCS
Block B	
Logical Memory I	NCS
Digit Backwards	NCS
Trail Making Test, Part A	NCS
Trail Making Test, Part B	NCS
Boston Naming Test	NCS
Logical Memory II	NCS
Additional Components	
Clinical Dementia Rating Scale—Participant	CDP
Neurologic History	NHX

**Note: For NCS, ARIC-shared participants will only complete the CERAD immediate recall and delayed recall tests.*

8.2 Brief Description of Cognitive Tests

8.2.1 Mini-mental State Examination Test (MMSE)

Overview: The MMSE is a brief, standardized instrument for screening a limited number of cognitive functions. 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 will include 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.

Administration: The MMSE will be administered by interview and should be attempted by all participants. A detailed script and QxQ is provided for each item and task. The total score will range from 0-30. Intersecting pentagons from the MMSE will be used as one of two measures of the visuospatial skill domain and scored as pass/fail.

8.2.2 Wide Range Achievement Test (WRAT)

Overview: The WRAT is a measure of academic achievement and is often used to provide an indicator of premorbid functioning.

Administration: Following instructions, the participant is handed a test card and asked to read the words on the card aloud. Responses are recorded on the paper form. The test is discontinued following 5 consecutive errors. Scores range from 0-70.

8.2.3 CERAD Immediate and Delayed Recall

Overview: A test of verbal memory where participants are asked to learn a 10-word list over three trials (Immediate subtest) and then must recall as many words as possible after about a3- to 4-minute delay (Delayed subtest).

Administration: The participant is presented with a stimulus card for each of 10 words. The examiner reads the word aloud and asks the participant to repeat the word. The participant is then asked to recall as many words as they can in a maximum of 90 seconds. This procedure is repeated 3 times. Following an approximate 5-minute delay, during which the (non-verbal) Digital Symbol Substitution Test (DSST) is given [or a break], the participant is asked to recall as many words as possible in 90 seconds. Scores range from 0-10 (total number of correctly recalled words) on each trial. Repetitions and intrusions are also recorded.

8.2.4 Digit Symbol Substitution Test

Overview: A test of executive function and psychomotor speed where participants are asked to relate numbers to symbols using a key. With a maximum score of 93, the participant's score is the number of correct symbol-number matches within 90 seconds.

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 a pencil (without an eraser). One point is given for each correctly drawn symbol completed within the 90 second time limit. Scores range from 0-93.

8.2.5 Incidental Learning

Overview: Adapted from the WAIS-R, incidental learning provides a non-verbal measure of recent memory.

Administration: Following the DSST, the participant is presented with an 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. Two scores are yielded: 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.

8.2.6 Word Fluency Test

Overview: A test of phonemic fluency, language, and executive function where participants are asked to generate as many words as possible beginning with the letter, “F,” “A,” and “S” within one minute.

Administration: Participants are 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. Proper nouns, variations, plurals, and repetitions do not count towards the total score. The score is the total number of admissible words produced across the letters.

8.2.7 Animal Naming

Overview: A measure of category fluency (semantic association).

Administration: Participant is asked to name as many different animals as possible within a 60 second time limit. The score is the total number of admissible animals.

8.2.8 Logical Memory

Overview: This test is part of the Wechsler Memory Scale—Revised version. It provides a measure of immediate and delayed verbal recall for the number of ideas presented in two stores which are read to the participant.

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 store as possible. The Logical Memory Score provides a measure of immediate recall and is calculated as the average number of ideas recalled from Story A and Story B. Each story contains 25 scoring units. The maximum score is 25 (25+25/2).

8.2.9 Digit Span Backwards

Overview: This test is also part of the Wechsler Memory Scale—Revised version. The Digit Span

Backwards test provides a measure of attention and working memory.

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 trails 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.

8.2.10 Trail Making Tests, Part A and B

Overview: The Trail Making Tests (TMT), Parts A and B, are timed tasks in which the participants connect letters and numbers in sequence as quickly as possible. The TMT measures attention, sequencing, mental flexibility, and visual search and motor function.

Administration: In TMT Part A, the participant is asked to draw a line and connect a series of numbers (from 1-25) as quickly as possible. In TMT Part 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 is allowed.

8.2.11 Boston Naming

Overview: The Boston Naming Test assesses visual naming ability using black-and-white drawings of common objects. The 30-item version used by the NACC Uniform Data Set will be used.

Administration: The participant is presented with a series of line drawings of objects and asked to name each object. The items become progressively 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.

8.3 Materials needed for Neurocognitive Testing

- Card with Pentagons and “Close your eyes” card (MMSE)—5x8
- MMSE Scoring Key for Spelling WORLD Backwards
- WRAT4 Reading Card
- Pencil
- Wrist Watch
- 1 Sheet of Paper
- Three sets of 10 words for CERAD Immediate—5x8
- Digit Symbol Substitution Form
- Digit Symbol Substitution Scoring Transparency
- Incidental Learning Template

- Set of 2 Trail Making Tests (A and B) on card stock per participant. Each card will have the sample on the front and the test on the back.
- Boston Naming Binder
- *Do Not Disturb* Sign for the door during the exam
- Audio Recorder
- Clipboard
- Stop Watch

8.4 Informant Interviews (Stage 2)

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 as part of the Exam 4 cognitive assessment), the CDR Informant (CDI, administered if participants are selected to Stage 2), 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, rather, all FAQ items are embedded within the CDR interview and recorded on the CDI.

8.4.1 Clinical Dementia Rating (CDR)

Overview: 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. Since participant 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 and allows the participants to report any symptoms of memory loss or memory impairment that he or she has noticed. The CDP is administered as part of Stage I to allow for all participants to complete the questionnaire. 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.

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 participant present. No equipment is required for administration. The CDR informant (CDI) is administered by the trained and certified examiner.

Administration: CDR summary score

The certified examiner will score the CDR after completing the two components (CDP and CDI), and will not score them in the presence of the participant or informant. A scoring algorithm will be taught to study staff based on the responses to the questions on both the CDR participant and the CDR informant; this will be completed in the event of a missing informant, as well.
The certified examiner will be primarily responsible for generating the CDR box scores, ranging from 0 (normal) to 3 (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 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; 3=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, and will only be used for research purposes and not be part of the classification or selection process.

The basic formula to generate a global CDR score is as follows: memory (M) is considered the primary category, with others considered secondary. The global CDR is the same as the M score if at least 3 secondary categories are given the same score as M; however, if 3 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 3 or more of the other categories are scored at a 1 or greater. If 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).

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 3 (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, 31, 35 (scored twice: covers two FAQ questions), 36, and 37. The total FAQ score, used for classification, is the sum of the 10 individual scores when all values are non-missing.

8.4.2 Neuropsychiatric Inventory (NPI)

Overview: 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 (from Exam 4) might increase the likelihood that apparent memory or other cognitive problems are actually due to depression, rather than dementia.

Administration: 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). The participant should not be present. No special equipment is needed.

8.5 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. The nature, severity, and frequency of sensory or other functional impairments (e.g., visual, hearing, literacy, limb or motor problem) may vary across participants. These impairments may affect several aspects of the examination, including the cognitive assessment. If a test was discontinued or not given due to an impairment, record the reason for discontinuation on the NCS summary form.

8.6 Training and Certification

Staff will be trained to a common level of proficiency in the administration and scoring of the neurocognitive measures. Following training, staff will obtain approval and submit 3 audiotaped neurocognitive assessments along with copies of the associated paper protocols to Lead Psychometrist at the ARIC Study at the University of Mississippi Medical Center for review. Certification assessments should not be performed on JHS participants. Staff certification for the neurocognitive battery exam is achieved by the successful administration and scoring of the 3 certification assessments reviewed and approved by the Lead Psychometrist at the ARIC Study to start (with a transition to JHS Lead Psychometrist for review). The JHS Lead Psychometrist is responsible for the basic training of all new examiners. Following basic training and approval by the lead examiner, 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, staff will administer the neurocognitive measures at least once per month. Recertification will be performed annually and requires the successful administration and scoring of one audio-taped neurocognitive examination for review and approval. An actual participant assessment may be submitted for recertification purposes.

8.7 Quality Assurance

8.7.1 Quality Assurance Stage 1

Several procedures are in place to monitor data quality. With participant approval, all assessments are routinely audio-taped for quality control. During the first month of the study, 2 audio-taped exams and associated paper protocols for each staff will be reviewed by the lead examiner to ensure appropriate pacing and technique, adherence to protocol, and accuracy of recorded responses and scoring. For months 2 and 3, 1 audio-taped exam and associated paper protocol for each staff will be reviewed by the lead trainer. Notes about any inconsistencies and deviations from the established protocol will be discussed with the staff. After month 3, the QC schedule is 1 recording due every other month. Follow-up phone reviews will occur as needed (i.e., if scoring errors occur and/or other significant errors with administration—following the scripts, prompting appropriately, etc.). General feedback pertaining to all staff is provided on monthly conference calls.

8.7.2 Quality Assurance Stage 2 (CDR and NPI)

Online training and certification for the CDR is required (www.adrc.wustl.edu). After selecting "Begin CDR Training", the user will be asked to register after which they will have access to 9 videos, each approximately 30 minutes in duration. The staff should plan to review these videos over several days. Two audio-taped recordings of the CDR interviews (Informant and Subject interviews) per staff will be reviewed by the Lead Psychometrist.

During the first 6 months of the study, 2 audiotaped sessions of the CDR interviews (CDR- Participant [CDP]; CDR-Informant CDI]) and associated documentation (pdf from REDCap for CDP, CDI, and CDR-Summary [CDS]), for each interviewer will be reviewed by the Lead Psychometrist. After the initial 6-month period, the Lead Psychometrist will review one session per interviewer, noting deviations from the standardized protocol.

9 PHYSICAL FUNCTION

The assessment of physical function incorporates aspects of strength, mobility, freedom of movement, balance, and coordination.

9.1 Overview

Staff should administer the individual components in the following sequence:

1. Explain the procedure to the participant using a standardized script.
2. Demonstrate the procedure to the participant.
3. Ask the participant if they have any questions.
4. Briefly explain the procedure once again.
5. Ask the participant to perform the procedure and begin all timed procedures with the words, "Ready? Go!"

Data will be entered in REDCap in the Physical Function Test (PFX) form. All questions in the PFX form should be coded as:

- 'Participant Refused' if the individual is unwilling to attempt performance of a task.
- 'Not attempted, unable' if it is not possible to perform the task or if the participant is unable to attempt performance.

Participants should be wearing comfortable walking shoes for the performance-based measures. Staff may wish to keep a supply of clean non-slip socks for participants who do not have comfortable shoes or who are more comfortable in socks.

9.2 Chair Stands

A straight-backed chair without arms, with seat height of approximately 18”, should be used for this test and placed against a wall for safety. Use the sturdiest chair that you can find. The staff may stand in front of the participant with arms extended (for the participant's safety) during the chair stands.

The single chair stand is used as a screener for the ability to do repeated chair stands with the following precautions:

- Walking aids, such as canes, walker, or crutches may not be used.
- The participant should be seated so that their feet rest on the floor.
- The participant’s back and buttocks should be against the back of the chair, if possible.
- If the participant uses a wheelchair and can get up from the wheelchair on their own, have them perform the maneuver from the wheelchair. Please ensure that the wheelchair is in the locked position. When performing the procedure, stand in front of the participant to assist if they lose their balance.
- The participant may not use their arms in this exercise.

If the participant is unable to rise without using their arms for assistance but was able to accomplish the task when arms were used, record that information in Question 1. If the arms come up or out, remind the participant not to use their arms and ask them to repeat the chair stand. If the arms still come up, score as "Rises using arms." Also record if the participant attempted, but was unable to rise. A rocking movement or shifting of weight is counted as an attempt. The repeated chair stands should be timed using the stopwatch.

9.3 Standing Balance

The participant is asked to do several stands in which ability to balance is measured. In these stands, the staff must demonstrate the position of the feet for the stand and measure the number of seconds for which the stand can be held. Remind the participant not to begin to do the stand until after it has been demonstrated. It is very important that the staff demonstrate the stand correctly as

participants tend to follow the demonstration rather than any verbal instruction given. If the participant indicates that they do not understand the stand, it may be demonstrated a second time.

Loss of balance can occur during the standing balance tests. During the demonstration, the staff should illustrate how to take a step if the participant loses their balance. For all participants, staff should stand next to the participant and offer the support of their arm. The participant should grab the staff member if needed because if the staff grabs the participant, this can put the participant at risk for a fall. If the participant is frail, additional safety precautions include:

- Staff should position themselves standing at the participant's side, slightly behind the participant. Staff's hands should be positioned at the participant's trunk at the hip or waist level but not touching the participant. Staff may wish to put one leg in front of the other in a lunge position for stabilization. Staff should describe to the participant that they are available to support them.
- If the participant loses balance, staff should immediately hold onto the participant with both hands at the trunk and stabilize them.
- If the participant begins to fall, staff should not try to catch them. Instead, staff should reach under the participant's shoulders from behind and slowly ease them down to the floor. A knee can be used if there is difficulty supporting the participant. This will prevent the participant and staff from becoming injured.

For each stand, staff will verbally describe the stand to the participant as they demonstrate it. If the participant feels it would be unsafe to try, they should not attempt to do it. Minimize any drama or emotion associated with being unable to complete a stand or falling out of a stand early. If the participant attempts the stand incorrectly, staff may demonstrate it again. As soon as the participant is in position and lets go of the staff's arm, time the stand.

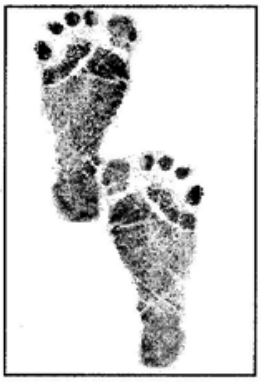
After 10 seconds, staff may tell the participant to stop. If the participant loses balance prior to the ten seconds, staff will record the number of seconds for which the stand was held.

Question 3 – Semi Tandem Stand:

Staff should allow the participant to hold onto their arm to get balanced. Then staff will say "When you are ready, let go of my arm." Staff will say "STOP" after 10 seconds. See **Figure 22** for placement of feet.

Figure 22

Placement of feet



If the participant is not able to hold the semi tandem stand for the entire 10 seconds, staff will go to Question 4 (side-by-side stand). If the participant is able to hold a semi tandem stand for 10 seconds, staff will go to Question 5 (tandem stand).

Question 4 – Side-by-side Stand:

Staff will allow the participant to hold onto their arm to get balanced. Then staff will say “When you are ready, let go of my arm.” Staff will say "STOP" after 10 seconds. Feet should be parallel and touching.

Question 5 – Tandem Stand:

Staff will allow the participant to hold onto their arm to get balanced. Then staff will say “When you are ready, let go of my arm.” Staff will say "STOP" after 10 seconds. See **Figure 23** for placement of feet.

Figure 23

Placement of feet

9.4 4-Meter Walk

To prepare the course for the measured walk test, first obtain a measuring tape that is greater than 4 meters (157.48 inches). It is important that the measuring tape not have any “give”, such that it cannot be stretched, causing the course length to vary. The course should be laid out on a hard surface (avoid carpet). Once the best course if found, tear off a 2- to 3-foot piece of duct tape and place down to indicate the starting line. It is recommended that the duct tape color be chosen to contrast with the floor. Place another piece of duct tape of similar length under the 4-meter mark. Once the start and end lines are laid down, the tape measure can be removed and the course is ready for use.

Loss of balance can occur during the 4-meter walk. The staff member’s arm can provide support if the participant loses balance. If the participant is frail, additional safety precautions include:

- Staff should position themselves standing at the participant's side, slightly behind the participant. Staff’s hands should be positioned at the participant's trunk at the hip or waist level but not touching the participant. Staff may wish to put one leg in front of the other in a lunge position for stabilization. Staff should describe to the participant that they are available to support them.
- If the participant loses balance, staff should immediately hold onto the participant with both hands at the trunk and stabilize them.
- If the participant begins to fall, staff should not try to catch them. Instead, staff should reach under the participant's shoulders from behind and slowly ease them down to the floor. A knee can be used if there is difficulty supporting the participant. This will prevent the participant and staff from becoming injured.

Occasionally, the participant will be so unsteady that the staff member will be concerned for their safety. In all instances, staff should be close enough to the participant to offer support if they should lose their balance or trip. The staff member may decide not to perform the test if the participant appears in imminent danger of falling. However, as a general rule, every participant should be encouraged to attempt the walk.

To measure the time it takes for the participant to walk 4 meters, the staff will use a stopwatch. The following guidelines are to be followed:

- Place the participant at the starting mark (toes lined up at the mark).
- Prepare the stopwatch. Staff should tell the participant to walk the length of the rule when they give the signal. Staff may walk alongside of the participant during the exercise, especially if loss of balance is a concern.
- Staff will note the exact time at which the participant's foot completely crosses the end of the rule. Staff will record the time it took to walk the distance in seconds to the nearest 0.01.
- If necessary, participants may use walking aids, such as a walker or cane.

Staff may ask participants who arrive with walking aids if they think they can do the short walk without the device, as many with aids will be both comfortable and capable of doing the walks without a walking aid. The 4-meter walk will be repeated two times.

Staff will start the stopwatch as the participant begins walking. The stopwatch will be kept behind the participant so they cannot see it. When the participant's first foot crosses the finish line, staff will stop the stopwatch. If the participant fails to cross the finish line, staff will explain the procedure again and repeat the process.

9.5 Grip Strength

The grip strength examination is used to test how strong the participant's hands are. Participants with one or more of the following conditions should not be tested:

1. Acute flare-up of wrist/hand; for example, arthritis, tendinitis, or carpal tunnel syndrome.
2. Less than 3 months after surgery on the hand or wrist.
3. If the staff has concerns that this test may exacerbate symptoms of heart disease (e.g., angina), the situation should be investigated. This does NOT exclude the participant from the grip strength test.

The chair should be at the proper height so that the table is between the participant's shoulder and waist. The participant will extend the arm to be tested forward and position it below shoulder level with the forearm resting on the table and the elbow just hanging off the edge of the table. An eraser or comparably sized rolled towel will be placed under the wrist. The dynamometer is held perpendicular to the table in the hand to be tested. Grip and positions are shown in **Figure 24**.

Figure 24

Grip Positions

- Allow one submaximal practice trial. *Note: dynamometer must be reset between trials.*
- Repeat the examination twice in the dominant hand, waiting about 15-20 seconds between each trial.
- Record the results of each trial before the next attempt.
- Record the strength for each attempt in kilograms, rounding to the nearest 2 kg. If it is exactly between two even numbers on dynamometer, round up. The dynamometer should be read at eye level.
- Reset to zero between trials.

9.6 Training

Staff should view the training videos for the chair stands, standing balance, 4-meter walk, and grip strength test every 6 months.

Chair stands, standing balance, 4-meter walk:
https://www.youtube.com/watch?v=N_rJOGhQgZ4

Grip Strength with Jamar Dynamometer**:** https://www.youtube.com/watch?v=frcNPiLnWRo

10 LOWER EXTREMITY EDEMA

Lower extremity edema is the noticeable swelling of one or both legs and can occur when fluid buildups in the leg. Physical examination of the participant's lower extremities will assess edema.

10.1 Edema Form

The results are recorded on the Lower Extremity Edema (LEE) form. A trained and certified technician performs a standardized examination of the lower extremities to assess and grade the presence of edema. To save time, this examination can be done just before or just after recording the echocardiogram since the participant will be lying on an exam table. The examination for lower extremity swelling can be also done before the pulse wave velocity examination but not afterwards, since pressure from the ankle cuffs may interfere with the assessment of swelling.

10.2 Examination Procedures

While the participant is lying on their back, socks will be removed in order to view the ankles and the tops of the feet (where "pedal edema" is located). Staff will avoid pressure to any areas with ulcers or sores (often due to poor circulation). Staff will apply gentle but firm pressure for a second or two with their thumb anteriorly along the mid-tibia (along the bony surface) down to the ankle in each leg, at 5 locations. With the staff facing the patient, staff will use their left hand/thumb for the right leg exam and right hand/thumb for the left leg exam. It is acceptable for staff to stabilize the leg by holding the back of the participant's ankle with the other hand.

Staff will look for pitting or indention that remains after pressure has been removed. If the indentation (pit) remains for more than two seconds, it is called “pitting edema.” Pitting above the middle of the lower leg (between the knee and ankle) is considered “marked.” If it only occurs below that point, it is considered “mild.”

The exam is repeated on the other leg. The appropriate findings are entered on the LEE form. If there has been an amputation, or a cast or other reason that prevents this examination, “not done” will be noted on the form and the reason.

10.3 Training and Certification

Certification requires familiarity with the protocol and equipment, and successful performance of the two components of the physical examination on five volunteers, inclusive of data entry and transfer, witnessed by the trainer.

10.4 Quality Assurance

After initial training and certification, continuing education is based on performance indicators monitored by the clinic manager and re-certification may be required.

11 ECHOCARDIOGRAPHY

An echocardiogram is an ultrasound of the heart, which provides live images of the heart’s movement. Echocardiogram protocol and procedures are detailed in **Manual 6 Echocardiography**.

A comprehensive 2D/3D echocardiogram is performed by centrally trained and certified sonographers. The images are transferred to the central Echocardiography Reading Center for evaluation and a review of clinical alert findings. Clinical alerts are reported to the field center for notification to the study participants and their health care provider, if instructed by the participant.

11.1 Echocardiogram Form

The Echo Procedure Completion (EPC) form is completed by the sonographer and used to document the completion of the echo test, any alert conditions noted by the sonographer, and follow-up actions during the exam visit.

11.2 Local Echo Findings

Sonographers performing echocardiograms will occasionally identify abnormalities that they consider important. These findings will include, but are not limited to, tamponade, aortic dissection, thrombosed or frankly dysfunctional prosthetic valve, pseudoaneurysm, intracardiac abscess or obvious vegetation, and intracardiac thrombus. These findings are further reviewed by local study

cardiologists for confirmation and possible cardiology referral before concluding the exam visit. The reading center will also be informed of these findings concurrently to facilitate an expedited analysis of the study.

11.3 Reading Center Report of Echo Alerts and Results

Study echocardiograms will be formally over-read by cardiologists affiliated with the reading center. Over-readers will be assessing study echocardiograms for critical abnormalities that may require clinical attention and impact study participant care and for standard clinically reportable measurements that will be used to generate clinical alerts.

Critical abnormalities identified by overreading cardiologists that would require emergent notification and arrangements for care will be reported within 24 hours of review to the coordinating center. It will also be communicated to the field center as an Immediate Alert Notification. Abnormalities that would trigger a critical result include, but are not limited to a) tamponade, b) aortic dissection, c) thrombosed or frankly dysfunctional prosthetic valve, d) pseudoaneurysm, e) intracardiac abscess or obvious vegetation, f) intracardiac thrombus.

Specific non-critical abnormalities identified by overreading cardiologists that would be important for the participant and physician to be aware of, but that do not necessarily require emergent care will be incorporated into the routine data transfers from the reading center to the coordinating center. Such findings include: a) moderate or greater mitral regurgitation, b) moderate or greater mitral stenosis, c) moderate or greater obstructive lesions of left ventricular outflow, including aortic stenosis and dynamic left ventricular outflow tract obstruction, d) moderate or greater aortic regurgitation, e) moderate to severe pulmonary hypertension, f) severe right ventricular enlargement. These abnormalities will be included in an integrated summary of research study results prepared for the participant.

The coordinating center will include limited quantitative data in an integrated summary of research study results for all participants. This will include three commonly used measures of cardiac structure and function: a) left ventricular ejection fraction, b) left ventricular diastolic diameter, and c) left ventricular wall thickness, along with reference values.

11.4 Training and Certification

Sonographers at the field center will undergo two days of on-site training performed by the Central Echocardiograph Reading Center. Training will focus on Exam 4 imaging protocol (including live supervised scanning on models), electronic image transfer, procedures for handling potential clinical alerts based on echocardiographic findings. To be certified, each sonographer must first submit two (2) certification studies performed in accordance with the protocol and transferred electronically to the central reading center for review and certification.

11.5 Quality Assurance

For each echocardiogram received by the reading center, quality feedback will be provided via email to the performing sonographer. In situations where concerns arise regarding the quality of a study submitted by the field center, this feedback will include technical instructions for quality improvement. A pattern of inadequate or poor-quality studies will prompt directed discussion by the reading center with the field center and, possibly, retraining. The reading center also holds monthly teleconferences with study sonographers to review common or persistent quality issues with study echocardiograms, and receive feedback from sonographers.

12 ELECTROCARDIOGRAPHY

An electrocardiogram (ECG or EKG) is a recording of the electrical signal from the heart. Electrocardiogram protocol and procedures are detailed in **Manual 5 Electrocardiography**.

Each participant will have one resting 12-lead electrocardiogram (ECG) recorded using GE MAC 3500 portable electrocardiograph. The images are transferred to the Central Electrocardiogram Reading Center for evaluation.

12.1 Equipment and Supplies

The equipment and supplies needed for recording and transmitting ECGs:

- GE MAC 3500 Electrocardiograph with its 10-lead acquisition module
- SD memory card
- MAC 3500 ECG paper
- Disposable silver chloride electrodes
- Felt tip non-toxic washable markers
- Reference guides for "Participant Data Entry" (see **Table 5**)
- GE MAC 3500 operation manual
- Alcohol swabs and gauze pads
- Cotton surgical tape
- HeartSquare

Table 5

Participant Data Entry

Category Listed on MAC 3500	**Entry to Machine by ECG Technician**
Last name	Do not enter the participant's last name. Enter JHS.
First name	Enter JHS exam visit number (04)
ID number	Enter the ID number given by the JHS (Jxxxxxx)
Visit	04
Date of birth	Enter 01 and participant's month and year of birth (01-mm-yyyy)
Gender	M or F
Technician ID	Staff ID#
Secondary ID	Enter same as ID number (Jxxxxxx)

12.2 ECG Form

The Electrocardiogram (ECG) form is completed by staff and used to document the completion of the ECG test, any alert conditions noted on the ECG printout, and follow-up actions during the exam visit.

The ECG Interpretation (ECI) form is completed by the local study cardiologists after the exam visit. These results are reported back in an integrated summary of research study results prepared for the participant.

12.3 Local ECG Interpretation

Because diagnostic statements printed on the ECG machine are not always correct and the central Electrocardiogram Reading Center provides monthly measurement reports to the coordinating center, local reading/screening of the ECGs to detect alert findings during the exam is essential for participant safety purposes.

The staff should look for the following in the printed diagnostic statement on top of the ECG printout for possible alert conditions:

- Ventricular tachycardia
- Idioventricular rhythm
- Acute MI
- Complete heart block
- Mobitz Type II AV block
- Sustained SVT (including multifocal atrial tachycardia and paroxysmal atrial tachycardia)
- Atrial fibrillation/flutter with HR > 100 bpm or < 50 bpm
- Atrial fibrillation > 100 bpm or new onset
- Sinus bradycardia ≤ 44 bpm
- Sinus tachycardia ≥ 140 bpm
- ST changes consistent with ischemia

These alert ECGs are further reviewed by local study cardiologists for confirmation and possible cardiology referral before concluding the exam visit. There are other significant ECG abnormalities that warrant treatment, but because they do not require prompt action or immediate notification to the participant, they are not included in the above list.

12.4 Training and Certification

Staff must complete a central training and certification process by the reading center before they are allowed to acquire study ECGs. To be certified, staff must acquire and successfully transmit three (3) good quality ECGs to the central reading center. The 3 ECGs should be performed on 3 different volunteers or on 1 volunteer provided that there is at least 30 minutes between each ECG**.** Recertification process is the same as the certification process and will be requested if deterioration of quality is observed.

13 ANKLE-BRACHIAL INDEX

The ratio of the ankle blood pressure to the arm blood pressure (measured at the brachial artery) provides a measure of lower extremity arterial disease (circulation problems). The ankle-brachial index (ABI) is reduced to less than 1.0 when there is obstruction to blood flow in the legs. The ABI is a non-invasive measure of atherosclerosis. The ABI is associated with atherosclerotic disease in other vascular beds and predicts cardiovascular mortality.

13.1 Equipment and Supplies

1. 8-megahertz Doppler pen prove with built-in speakers
2. 9-volt alkaline batteries
3. Doppler conducting jelly
4. Standard mercury column sphygmomanometer: Wall-mounted Baumanometer
5. Calibrated V-Lok BP cuffs in four sizes:
    - 4 large adult cuffs
    - 8 regular adult cuffs
    - 4 small adult cuffs
    - 4 thigh cuffs
6. Tissues to remove conducting jelly
7. Black eyeliner pencil
8. Tegaderm

13.2 Exclusions

The below exclusion items are intended to determine the presence of any reasons the ABI measurements cannot be completed.

1. Persons with any open wounds in the ankle or arm cuff area (with the exception of lesion due to venous puncture due to a blood draw).
2. Persons with rigid arteries such that an occlusion pressure cannot be reached. If the artery cannot be occluded before the sphygmomanometer reaches 300 mmHg, the participant is excluded.
3. Persons with bilateral amputation.
4. Persons unable to lay at <45° angle.
5. Persons who have had a double mastectomy.

13.3 Equipment Maintenance

After completing the ABI measurements, thoroughly clean the Doppler probe and cuffs with Clorox Disinfecting Wipes. Please note that the Doppler must be completely clean and dry between participants.

13.4 Training and Certification

The technician must be certified with training in the proper operation and application of the blood pressure apparatus and doppler using standardized technique. Trainings include:

1. A thorough review of the forms, instructions, and protocol
2. Demonstration of appropriate techniques
3. Practice in the use of the apparatus on volunteers
4. Practice dealing with problem situations
5. Practice handling participants' comments and recording relevant information on the note logs
6. Review of post-interview responsibility for the ABI data
7. Compare measurements with those made by trainer (Goal: obtain measurements within ± 2 mm Hg of that observed by a trainer)

Each trainee must do at least three live readings with the trainer observing and listening to the Doppler. The readings at each site must agree within 4 mmHg and the average must agree within 3 mmHg. Re-certification is completed biannually and requires the completion of ABI measurements on two separate volunteers with replicate measures obtained for each. Agreement within 4 mmHg on any one reading, (systolic or diastolic) and averages should agree within 3 mmHg.

14 PULSE WAVE VELOCITY (PWV)

All measures for arterial stiffness will be calculated and recorded using the Vicorder® System (Skidmore Medical, Bristol, UK). The device measures PWV, the central (carotid) blood pressure, and other key hemodynamic variables in the pulse wave analysis, and thus reduces participant and staff burden. Once the sensors are in place, measurements can be repeated during the session for better data quality and to reduce measurement variability. PWV protocol and procedures are detailed in **Manual 19 Pulse Wave Velocity**.

14.1 Exclusion Criteria

- Unwillingness to have cuff placed on arm, thigh, or neck;
- Absence of bilateral lower extremities (above the knee);
- Any contraindication to having a blood pressure cuff inflated on an extremity (lymphedema, paresis/paralysis, arterial or venous lines, dialysis shunts, recent surgical wounds, mastectomy).

14.2 Workstation and Supplies

The Vicorder is intended to run under the control of the Vicorder software and is run from a PC laptop via a USB link (**Figure 25**). The Laptop USB link also provides power to the Vicorder. The PWV

workstation includes the Vicorder device, a laptop, a RossCraft segmometer, a wedge to incline the participant's shoulders and head, and the following supplies:

1. Blood pressure cuffs and neckband
2. Pressure hoses and connectors
3. Mild detergent and water solution (1:9 solution) to wipe neck band bladder after each participant
4. Black marker to mark the carotid palpation site
5. Alcohol swab/wipes to clean the participant's neck and wipe black marks
6. Plastic wrap to cover skin if alcohol cannot be used
7. Hand inflator, manometer, and manifold for calibration
8. Stopwatch or clock to monitor waiting periods
9. Disinfectant and alcohol wipes or spray to clean study surfaces after each participant
10. Step stool for participants to get on/off the examination table if needed

Figure 25

The Vicorder

14.3 PWV Form

The Pulse Wave Velocity (PWV) form is used to collect measurements that are input into the Vicorder program. The measurements collected on this form are keyed directly into REDCap (the weight and height will auto-populate into the PWV form from the ANT form). The staff then enters the participant's year of birth (item 1), month of birth (item 2), weight (item 3), height (item 4) and the difference (item 7) into the PWV data system in the Vicorder program.

14.4 Training and Certification

Staff are trained centrally. A combination of didactic presentations and hands-on practical demonstrations and practice of the vascular testing device are conducted. After staff has completed at least 10 measurements (preferably with volunteers of different body types), a site visit by the central trainer will be conducted. Staff will be evaluated during the direct observation of testing of participants. Suboptimal quality testing sessions and protocol violations will be reviewed and

discussed during the site visits, and these points will be reinforced later in a written report.

Following training, staff will be certified after successfully demonstrating calibration checks, blood pressure cuff and neckband placement, care and maintenance of the equipment, and data transfer. To retain certification, staff must collect good quality data on at least 6 participants each month during the examination period. Certification of new staff after the initial central training may be performed by a certified technician.

In the event of an extended pause in study measurements for more than two months (i.e., due to safety during a pandemic), staff will attend a virtual refresher session before resuming in- person visits. Prior to the session, staff should review the PWV MOP, watch the short Vicorder refresher video (https://youtu.be/MrdiBsPw8z4), and perform at least 2 PWV measurements.

14.5 Quality Control

Every month all PWV records with values < 5.5 m/s or > 15 m/s ("outliers") will be reviewed and graded by the central trainer. If the number of outliers was fewer than ten (10), a random sample will be selected (stratified by staff) to make 10 per month selected. The results will be shared with the field center staff.

15 ZIO PATCH

Participants will undergo up to 14-days of continuous cardiac monitoring to identify subclinical arrhythmia. At the end of the 14-day wear period, the participant will return the Zio Patch directly to the company (iRhythm) in a prepaid mailing box. Zio Patch protocol and procedures are detailed in **Manual 20 Atrial Fibrillation**.

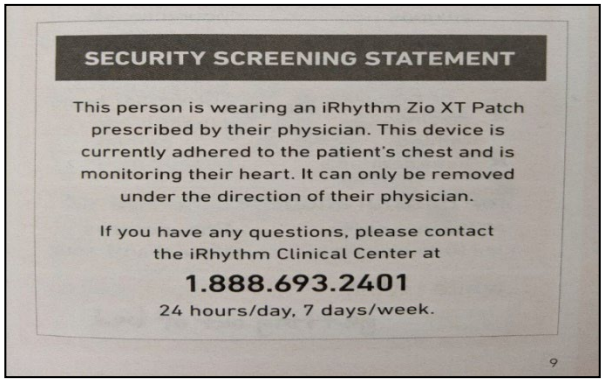
15.1 Exclusion Criteria

- A history of allergy to skin adhesives;
- Unwillingness to shave upper left chest;
- Implanted electronic devices including nerve stimulator, cochlear implant, or infusion pump are NOT OK to use with the Zio Patch. However, pacemakers or defibrillators (AICD) ARE OK for heart monitoring; the Zio Patch will not interfere with the pacemaker or defibrillator.
- Participants who have a job where they may be exposed to a large magnetic field.
- External cardioversion/defibrillation.

Note: If the participant has an upcoming MRI, CT scan, or mammogram, the scan should be scheduled after completing cardiac monitoring with the Zio Patch. It is possible that the Zio Patch would be detected at an airport by TSA screening. The Zio Patch booklet includes a statement for the participant to show TSA personnel if the patch is detected. However, if the participant knows they will be traveling by air, it would be best to reschedule the Zio Patch after or around the air travel (**Figure 26**).

Figure 26

Security Screening Statement from Zio Patch Booklet

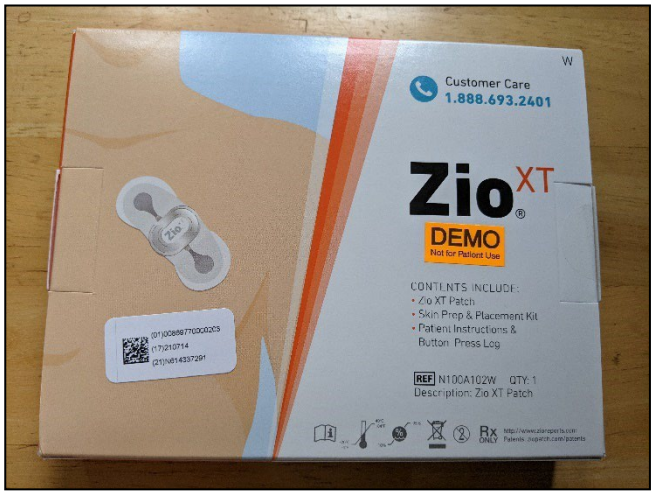


15.2 Equipment and Supplies

- Zio Patch monitor kit (**Figure 27**)
- Spare demo Zio Patch to use for demonstration
- Gown
- Gloves
- Timer
- Roll of microporous tape

Figure 27

Zio Patch monitor kit



15.3 Zio Patch Form

The Zio Patch Screening Questionnaire (ZRE) is completed by the field center staff to document participant eligibility.

The Zio Patch Completion Form (ZPC) is used by the field center to record device application/re-application (if necessary), as well as check-ins and reminder calls following device application.

The Zio Patch Reviewer (ZDX) form is completed by the EPICARE overread physician to classify Zio Patch results as (a) alert conditions present, (b) no alert conditions but abnormal findings present, or (c) within normal limits.

15.4 Alerts and Results Reporting

For each Zio Patch received by iRhythm, a written report and selected heart rhythm tracings are placed by the iRhythm technician on the iRhythm HIPAA-compliant server. The EPICARE ECG Reading Center staff members are notified by iRhythm staff within 24 hours if an Alert condition (listed below) is detected by the iRhythm technician. For participants both with and without alert conditions, the EPICARE reader downloads the iRhythm report and selected tracings from the iRhythm server to an EPICARE server and conducts a physician over-read of the results. The EPICARE reader then completes the ZDX form classifying the report as (a) alert conditions present, (b) no alert conditions but abnormal findings present, or (c) within normal limits.

If there is an alert condition, notification is sent via email to Field Center staff, Coordinating Center staff, and the ancillary study PI and the Field Center manager follows up with the participant promptly. For participants who do not have alert conditions but have abnormal results, a results letter listing abnormal findings and the first page of the Zio Patch report will be mailed to the participant. For participants who do not have alert conditions or abnormal results, a results letter that states “No abnormal findings were detected” will be mailed to the participant.

Alert conditions:

1) Wide QRS tachycardia > 120 beats per minute (bpm) and sustained for > 30 seconds (includes ventricular tachycardia and ventricularfibrillation)
2) Complete heart block
3) 2nd degree AV Block, Mobitz II
4) Pause > 6 seconds
5) Bradycardia < 40 bpm and sustained for > 30 seconds
6) Atrial fibrillation with average heart rate < 40 bpm or > 180 bpm and sustained for 60 seconds
7) Narrow QRS tachycardia > 180 bpm and sustained for 60 seconds
8) Other findings of concern to EPICARE reader.

Abnormal results:

1) Pause of >3 seconds duration at an <u>overall rate</u> of 1 or more per day, or more than 3 pauses in a single day.
2) Supraventricular tachycardia (SVT), defined as 4 or more consecutive premature atrial contractions (PACs), occurring at an <u>overall rate</u> of 2 or more per day, or a single episode of SVT lasting >15 sec with an average rate of >120 bpm

3) Supraventricular: ectopy (single PAC) >1%; couplets >1%, or triplets>1%
4) Ventricular tachycardia (VT) occurring at an overall rate of 1 or more per day, or a single episode of VT lasting >5 sec with an average rate of >120 bpm
5) Ventricular: ectopy (single premature ventricular contraction) >1%, couplets >1%, or triplets >1%
6) Atrial fibrillation of duration > 30 seconds
7) Atrial flutter of duration > 30 seconds
8) 2nd degree AV block, Mobitz I (Wenckebach)
9) Other findings of concern to EPICARE reader

For abnormal findings numbered 1, 2, and 4, the overall rate of pauses and episodes of SVT and VT will be reported as the number of occurrences divided by the number of days of analyzable rhythm.

15.5 Training and Certification

Staff will complete the following to become certified in applying the Zio Patch:

- Attend study training session.
- Successfully complete the registration of a participant on the iRhythm website.
- Apply a demo Zio Patch on a volunteer and provide all the participant information as directed in the protocol.
- Those who miss the training session must attend a virtual training with iRhythm, complete the registration of a participant on the iRhythm website and complete the application of a demo Zio Patch on a volunteer with the lead technician.

16 SENSORY TEST

The sensory test will assess pressure threshold and conditioned pain modulation. Participants with pain issues will be ineligible.

16.1 Equipment and Supplies

- Pressure Algometer (FDIX25 digital algometer)
- Blood pressure cuff
- Stress ball
- Stop watch (+/- metronome or metronome app on smart phone set to 60 beats per minute, with no time signature or ¼ time)
- Pen or maker for anatomic location marking
- Chair without wheels

16.2 Examination Procedures

Sensory testing will be assessed in a standardized manner using an algometer to assess pressure pain

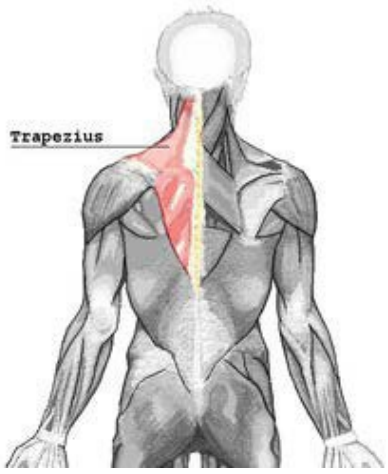
threshold (PPT) and conditioned pain modulation (CPM) at the upper trapezius muscle. Testing should be performed once the participant has had an opportunity to rest quietly for 2 minutes.

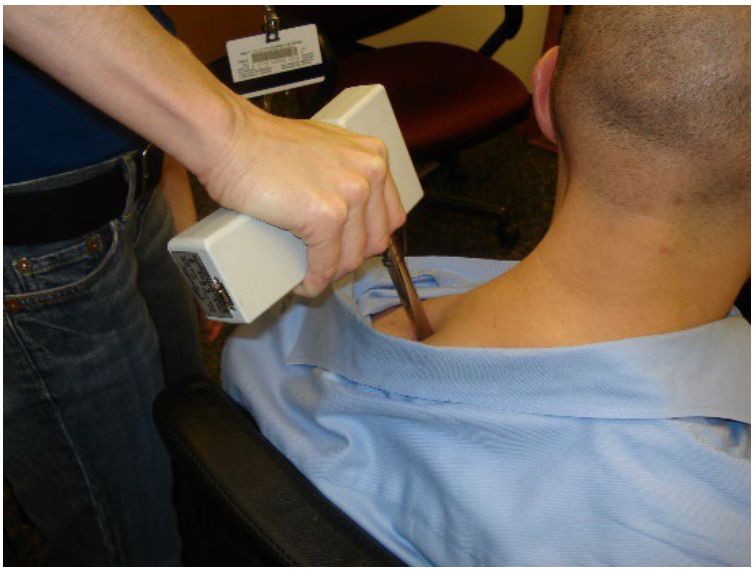
Before starting any procedure, and before performing anatomic landmarking, determine which trapezius is eligible for testing, and most importantly, which arm will have the blood pressure cuff administered based on both the trapezius exclusions and the blood pressure cuff exclusions. The trapezius contralateral (*i.e.*, opposite) to the arm to be used for blood pressure inflation must be used for all of the procedures below. If both arms are eligible, perform testing on right trapezius (with left arm to be used for blood pressure cuff inflation).

Anatomic sites for testing will need to be marked. The approximate center of the trapezius will be identified with a black make-up pencil by placing an 'x' to facilitate testing. The trapezius is a broad, flat, superficial muscle extending from the upper neck to the shoulder, and down to the mid-back. Pressure pain testing on the trapezius should be done between the neck and deltoid, with algometer tip pointed downward at the mid-point between the neck and edge of the shoulder (**Figure 28**). The participant should be in a gown/robe with the collar loose enough that the tip of the algometer can be applied to the trapezius.

Figure 28

Neck and edge of shoulder





16.2.1 Determine Testing Location

The pressure pain threshold (PPT) assessment will be performed at the ***right*** trapezius, unless exclusions require the left side to be used.

Before initiating the quantitative sensory testing, the examiner should have already determined eligibility for including the conditioned pain modulation (CPM) protocol with the PPT assessment, which is primarily related to blood pressure cuff inflation. The CPM protocol requires blood pressure cuff inflation, preferably in the left arm; if there are exclusions for using the left arm, then the right arm can be used. *Please note: if the right arm must be used for blood pressure cuff inflation, then the LEFT trapezius should be used for PPT and CPM.*

Exclusions for PPT

- Any recent (< 6 weeks) trauma/injury to the right or left trapezius will preclude PPT assessment on that side.

Exclusions for CPM

- MI within 6 months.
- Severe peripheral vascular disease.
- Any exclusions that were relevant for blood pressure measurement.
    - *Exclusions for left arm BP measurement (then use right arm for blood pressure cuff inflation and left trapezius for PPT and CPM).*
        - Lymphedema (*e.g.*, post-mastectomy for breast cancer).
        - Takayasu's arteritis (regardless of disease activity) (because this disease result in pulselessness/poor blood flow due to arterial narrowing).
        - Arteriovenous fistula for hemodialysis.

16.2.2 Prepare the Algometer

To prepare the algometer (**Figure 29**), ensure the arrows point to 'C', to "Peak" (use Scroll/Peak button to set this), and to "kgf" (use Escape/Units buttons to set this). Hit 'Select/Zero' button in between readings (after having recorded the reading on the data collection form).

Figure 29

Algometer

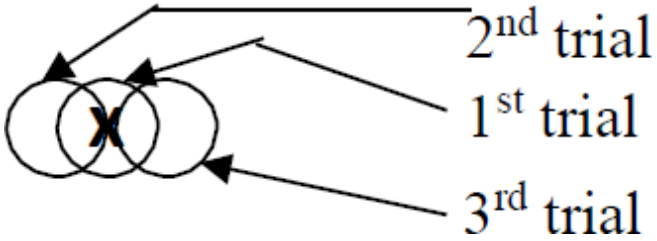
16.2.3 Pressure Pain Threshold (PPT)

Repeat the PPT test three times. For the 1st trial, center the rubber tip over the 'x' that is marking the site to be tested. For the 2nd trial, move the center of the rubber tip slightly to the left such that the right edge of the rubber tip is in the middle of the 1st circle. For the 3rd trial, move the center of the

rubber tip to the right such that the left edge of the rubber tip is touching the right side of the 2nd circle and is in the middle of the 1st circle (**Figure 30**).

Figure 30

Circle diagram



Ensure that the examiners arms are supported (*e.g.*, both elbows tucked in at the examiners sides) since 'free' arms are more prone to movement and it is more difficult to control the pressure algometer. This will require standing behind the participant's shoulder. The device should be held with both hands on either side of the device and thumbs on the top to provide adequate control and pressure.

Place the tip of the algometer perpendicular to the skin and apply steady and increasing pressure at a rate of 0.5 kg/sec starting at 0; use a metronome with ear-piece as needed.

Record the pressure reading at the point at which the participant reports "pain" on the data collection form and remove the algometer from skin at that point. If 10 kg is reached on the algometer without the participant reporting "pain," terminate the trial and record as 9.99 kg.

16.2.4 Conditioned Pain Modulation (CPM)

Immediately upon completing the three PPT trials at the trapezius, the CPM protocol will be initiated. If the right trapezius had PPT assessed, then the left arm should be used for blood pressure measurement.

Elevate the index arm to chest level. Place the blood pressure cuff around the middle of the upper arm for blood pressure measurement, with the lower edge of the cuff approximately 3 cm proximal to the antecubital fossa. Inflate the cuff to 10 mm Hg above the systolic blood pressure that was already recorded on the SBP form (should be auto-populated from the SBP form). If it was not recorded, then inflate the cuff to 10 mm Hg above the loss of the radial pulse being palpable.

Start the timer set to 2 minutes. Ask the participant to squeeze the stress ball 10 times at a rate of one squeeze per second and then rate their pain on a scale from 0-10.

i. If pain is < 4, ask the participant to continue with another set of 10 hand exercises; repeat pain rating and hand exercise as needed until conditions in ii, iii, or iv occurs.
ii. If pain ≥ 4, the participant can discontinue hand exercises and go to PPT.
iii. If pain is unbearable and the participant requests cuff deflation. Deflate cuff and go to PPT.
iv. If cuff has been inflated for 2 minutes without pain ≥ 4. Go to PPT.

Record number of hand squeezes required prior to proceeding to PPT. If the participant does more than 99 hand squeezes, record 99 on the form.

Record pain rating prior to proceeding to PPT.

Record PPT at the trapezius (opposite to the arm with the blood pressure cuff inflated). Perform 3 PPT trials as per the initial assessment. Unless the pain is unbearable and the participant requests cuff deflation (see iii above), the cuff remains inflated on the participant's arm while the PPT is assessed. Deflate the cuff upon final PPT measurement. Record the time the cuff was inflated, and whether the 2nd round of PPTs were obtained with the cuff deflated.

16.3 Pain Sensory Form

Pain and Sensory Testing (PST) form is used to determine exclusions for pressure pain threshold test and blood pressure measurement and to record results of PPT and CPM.

Community Assessment of Pain (CAP) form is a questionnaire used to collect data on participant's experience of pain. These include general pain questions, pain interference with various aspects of life, thoughts/feelings of pain, location of pain (joins, body regions), pain severity, and pain patterns.

6.4 Training and Certification

Certified trainers will train the field center staff who will be administering the quantitative sensory tests. Field center staff require no special qualifications or experience to perform this testing. Staff will be initially certified following the below certification requirements. The PPT exam will require a second certification by the certified trainer. Staff will be retrained and recertified midway through each examination cycle.

Training should include:

- Read and study manual.
- Attend training session on techniques (or observe administration by examiner).
- Practice on other staff or volunteers.
- Discuss problems and questions with local expert or QC officer.
- Suggestion: Use metronome for training pressure algometry.

Certification requirements:

- Complete training requirements.
- Pass algometer calibration test (5 kg at 10 seconds +/- 1 second and 7 kg at 14 seconds +/- 1 second).
- Conduct exam on two volunteers according to protocol, as demonstrated by QC checklist.

17 BRAIN MAGNETIC RESONANCE IMAGING (MRI)

The brain MRI will be performed on a separate day. During Exam 4, eligibility will be determined and all eligible participants will be scheduled for a brain MRI. Brain MRI protocol and procedures are detailed in **Manuals 17a and 17b**.

17.1 Form MRE

The MRI Recruitment and Eligibility Form (MRE) is completed by the field center staff to document participant eligibility. The MRI Procedure Completion Form (MPC) is used by the field center to record MRI attempts, completion, no shows for scheduled appointment, and decline to proceed with the MRI after initially agreeing.

The Local MRI Report and Referral Form – Brain (LMR) is completed by local radiologists to document alerts, abnormal findings (physician notification or follow-up recommended), and incidental findings (that do not require physician notification).

17.2 Local Reporting of MRI Results

The results recorded on the LMR forms are used by the coordinating center for routine reporting of MRI results to the participants. If there were any alerts or abnormal findings present, the radiology staff will alert the clinic manager by phone or via text on a dedicated cell phone for imaging. Participants will be notified by the clinic manager within 24 hours of any urgent alerts or conditional urgent alerts and within 72 hours of any abnormal findings that require physician notification.

17.3 Reading Center Reporting of MRI Results

The MRI reading center transfers all MRI findings to the coordinating center on a quarterly basis. However, if there are any alerts present, the reading center will notify the coordinating center and clinic manager via email within 7 days of the receipt of the MRI images. These reading center alerts are compared with local radiology findings by the clinic staff. Any discrepant alert findings between the reading center and local radiologists are discussed with the PI of the coordinating center and local radiologists to determine follow-up actions on a case-by-case basis.

17.4 Quality Assurance

Prior to any participants being scanned, the site's scanner must complete MRI site qualification. In most cases, site qualification will only involve scanning a phantom with the electronically provided

JHS sequences, which is provided by the MRI reading center and loaded by the local service engineer. Once the scan is received, the reading center QC team will review the scanned protocols for correct parameters, good image quality and scanner performance. If the scans do not pass QC, the site will be asked to re-scan after making the suggested changes by the reading center QC team. After successful qualification scanning, the reading center will send an official Site Certification e-mail to notify JHS that their site has been approved and is ready to scan study participants.

18 INTERVIEWS

Specific instructions for completing each item on the data collection form are given in the QxQ instructions for the form. For all interviewer-administered questionnaires, questions should be read to the participant verbatim as they appear on the form to ensure standardization. In addition, any introductory and transitional wording should be read verbatim. Cue cards may be created and used during the interview to prompt and remind participants of their response options as necessary.

18.1 Medication Survey

The medication survey is used to ascertain medication usage by coding prescription and nonprescription drugs, home or folk remedies, used by the participant within the four weeks preceding the interview.

The Medication Survey Form A (MSA) ascertains whether the participant has brought in all medications taken within the last four weeks, medication names, and medication strength/units. The Medication Survey Form B (MSB) ascertains whether any medications were used to treat cardiovascular diseases or symptoms and medication taking behaviors.

MSA is completed during the consent process. The staff determines and records whether the participant has brought in all medications taken within the last four weeks. Identification labels are placed on the participant's medication bag and the MSA. If the participant has not brought in any (all) medications, inquiries are made to differentiate between non-compliance with pre-visit instructions or non-use of medications in the prior four weeks. In case of inadvertent omissions, arrangements are made for obtaining the information, usually by telephone interview.

The name on the medication bag is checked against the name on the MSA. When preparing to ask the participant about each medication, the interviewer removes all containers from the bag and sets them in front of the participant. As each medication is reviewed, it is shown to the participant while keeping the other medications in view. After the participant answers the questions for each medication, its container is placed back in the carrying bag to minimize confusion and to assure that all medications are returned.

When there are more than 26 medications, recording the name and strength/unit is continued on the back of the page if a paper form is used. If more than 26 medications need to be entered into REDCap, the name and concentration of the additional medications are written on a piece of paper labeled with the participant's ID and filed in the participant's folder for future coding. If the name of

the medication exceeds the number of fields in REDCap, the name is abbreviated.

When more than 26 medications have been recorded, the priority algorithm for data entry of the medications is as follows: prescription medications first; aspirin and aspirin-containing medications (e.g., aspirin, Alka Seltzer®, headache powders, cold medications, medication for arthritis); anti-inflammatory drugs (e.g., ibuprofen, Motrin®, Nuprin®); then over-the-counter medications, followed by vitamins and food supplements.

The interviewer verifies the transcription of medication names and makes corrections on the paper form and in REDCap as required.

18.1.1 Medication Coding

The six-digit medication code number is listed in a hard copy or REDCap version of the Medication Coding Dictionary. The Medispan code can be matched to the drug name while transcribing the name of the drug in REDCap or can be ascertained later.
Drug names are listed alphabetically. The medication code of a drug not listed in the dictionary is left blank, and its status code is always set to "Q" (questionable) so that the Coordinating Center can develop a code number and update the dictionary.

18.1.2 Quality Assurance

Certification to administer the MSA and MSB is achieved by the demonstration of adequate technique on 5 taped interviews, reviewed and approved by the Field Center Manager. Re-certification is required annually and requires the successful completion of one taped interview of an actual participant.

Quality assurance for medication coding is accomplished by coding a set of selected medication names and blinded recoding of 10% medications recorded during the previous year by the medication coders annually.

18.2 Food Frequency Questionnaire

The Food Frequency Questionnaire (FFQ) is a modified version of the Delta NIRI (Nutrition Intervention Research Initiative) FFQ. The FFQ was administered at the baseline JHS visit. Participants will be asked to provide information on both the frequency and portion of their usual intake of food items listed on the FFQ. Cue cards with frequency measures and standard portions will be used during the interview to prompt and remind participants of their choices. Selected food models will also be available to provide additional support for portion estimations.

At the completion of each interview, the interviewer will review the questionnaire for missing or improbable data and clarify any areas of concern. If there are missing data in the FFQ, staff should contact the participant for complete data. If the participant is unable to answer or cannot be contacted, then the missing data should be recorded as "never eaten" and specific notes to this

effect should be entered in comments field for future reference. *Note: all data must be filled in to get a complete FFQ analysis.*

18.2.1 Quality Assurance

The FFQ is administered by staff who have completed a required training program. Certification requires demonstration of adequate technique on 5 FFQs with annual recertification. Routine quality assurance is done by means of observation by the Field Center manager.

FFQ data is transferred to UMass Lowell for analysis on a quarterly basis. Batch checks of the dataset will include checks for outliers of nutrient totals, gram weights, frequency and serving sizes.

18.3 Women's Health History

The Women's Health History (WHX) is administered by certified interviewers to assess reproductive health. The WHX form collects data related to pregnancy outcomes (number of live births, preterm birth, birth weight), pregnancy complications (preeclampsia, gestational hypertension, gestational diabetes) and reproductive history (menstrual cycle, hot flashes/night sweat, hysterectomy, oophorectomy).

18.4 Personal Health History

The Personal Health History (PHX) form is used to update information on the personal health history of each participant. Participants rate their health status and self-report whether they have a history of various health conditions (e.g., hypertension, stroke, lung disease, peripheral arterial disease) and weight history.

18.5 Sleep Questionnaire

The sleep questionnaire (SLE) is administered to obtain information on the participant's self- report of quality and quantity of sleep, snoring, sleep disordered breathing, daytime sleepiness, and clinician-diagnosed conditions such as sleep apnea or obstructive sleep apnea, insomnia, and restless legs (Buysse et al., 1989; Johns, 1991).

Citations:

Buysse, D. J., Reynolds III, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193-213.

Johns, M. W. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*, *14*(6), 540-545.

18.6 Sociodemographic Data

The Sociodemographic (SDS) form is used to update participants' marital status, employment status, income and occupation, and household wealth.

18.7 Tobacco Use

The Tobacco Use (TOB) form is used to collect data on the type and frequency of tobacco use in the past 12 months. These include use of smoking tobacco (cigarettes, cigars, pipe, hookah), smokeless tobacco (chew or dip), and e-cigarette or other vaping devices.

18.8 Physical Activity

The Physical Activity Survey (PAC) is designed to obtain information about participant's physical activity habits during the past 12 months. The PAC contains 4 sections: "Active Living," "Occupational Activities," "Home, Family, Yard and Garden" and "Sports and Exercise." Participants are asked to identify the frequency and duration for these activities. For the sports/exercise section, respondents are also asked to identify the frequency and duration for the three most frequent sports/exercise activities performed in the past year (Smitherman et al., 2009).

Citation: Smitherman, T. A., Dubbert, P. M., Grothe, K. B., Sung, J. H., Kendzor, D. E., Reis, J. P., ... & Taylor, H. A. (2009). Validation of the Jackson Heart Study physical activity survey in African Americans. *Journal of Physical Activity and Health*, *6*(s1), S124-S132.

18.9 Psychosocial Instruments

The Psychosocial Instruments (PSI) include five sections: chronic burden, optimism, life satisfaction, purpose in life, and resilience.

- Chronic Burden (CBF) is a 5-Item scale assessing the effects of everyday stress. Participants report experiences of stress due to difficulties for six months or more. For each difficulty experienced, the severity of the situation (not very stressful, moderately stressful, very stressful) is also reported (Bromberger & Matthews, 1996).

  Citation: Bromberger, J. T., & Matthews, K. A. (1996). A longitudinal study of the effects of pessimism, trait anxiety, and life stress on depressive symptoms in middle-aged women. *Psychology and Aging*, *11*(2), 207.

- Optimism (LOT-R: Life Orientation Test-Revised) is a 10-item scale measuring how optimistic or pessimistic people feel about the future. The PSI includes only the 6 items of the LOT-R that are analyzed (without the filler items) (Scheier et al., 1994).

  Citation: Scheier, M. F., Carver, C. S., & Bridges, M. W. (1994). Distinguishing optimism from

neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *Journal of Personality and Social Psychology*, *67*(6), 1063.

- Life satisfaction (SWLS: Satisfaction with Life Scale) is a 5-item scale measuring life satisfaction (Diener et al., 1985).

  Citation: Diener, E., Emmons, R. A., Larsen, R. J., & Griffin, S. (1985). The Satisfaction with Life Scale. *Journal of Personality Assessment*, 49, 71-75.

- Purpose in Life (PIL) is a 7-item purpose in life subscale of the Ryff Psychological Well- being Scales (Ryff, 1989).

  Citation: Ryff, C. D. (1989). Happiness is everything, or is it? Explorations on the meaning of psychological well-being. *Journal of Personality and Social Psychology, 57*(6), 1069-1081.

- Resilience (BRS: Brief Resilience Scale) is a 6-item scale measuring an individual's ability to bounce back, resist illness, and adapt to stress or thrive in the face of adversity (Smith et al., 2017).

  Citation: Smith, B. W., Dalen, J., Wiggins, K., Tooley, E., Christopher, P., & Bernard, J. (2008). The brief resilience scale: assessing the ability to bounce back. *International Journal of Behavioral Medicine*, *15*, 194-200.

18.10 Global Chronic Stress

Global chronic stress is measured using the Global Perceived Stress Scale (GPSS) and recorded on the Global Chronic Stress (GCS) form. The GPSS is an 8-item, self-reported measure of global stress that assesses global perceptions of stressors associated with ongoing or enduring stressful conditions, such as employment, relationships, neighborhood, caring for others, legal problems, medical problems, experiences of racism and discrimination, and meeting basic needs (Bromberger & Matthews, 1996; Cohen et al., 1983; Payne et al., 2005).

Citations:

Bromberger, J. T., & Matthews, K. A. (1996). A longitudinal study of the effects of pessimism, trait anxiety, and life stress on depressive symptoms in middle-aged women. *Psychology and Aging*, *11*(2), 207.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, 385-396.

Payne, Thomas J., Sharon B. Wyatt, Thomas H. Mosley, Patricia M. Dubbert, Mary Lou Guiterrez-Mohammed, Rosie L. Calvin, Herman A. Taylor, and David R. Williams. "Sociocultural Methods in the Jackson Heart Study." Ethnicity & Disease 15 (2005): 38-48.

18.11 Depressive Symptoms

Depressive symptoms are assessed using the Center for Epidemiological Studies Depression 20- item scale (CESD-20) and recorded on the Depressive Symptoms (CES) form. The CESD-20 gathers data on symptoms of depression in nine different groups defined by the American Psychiatric Association Diagnostic and Statistical Manual (5th edition). These symptom groups include sadness (dysphoria), loss of interest (anhedonia), appetite, sleep, thinking/concentration, guilt (worthlessness), tiredness (fatigue), movement (agitation), and suicidal ideation (Radloff, 1977).

Citation: Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385-401.

18.12 Anger Expression Inventory

Anger expression is measured using Spielberger Anger Expression Inventory, a 16-item scale assessing anger-in (8 items) and anger-out (8 items), and recorded on the Anger Expression Inventory (AEI) form (Spielberger, 1985).

Citation: Spielberger, C. D. (1985). "The experience and expression of anger: Construction and validation of an anger expression scale." *Anger and Hostility in Cardiovascular Behavioral Disorder*: 5-30.

18.13 Diabetes Questionnaire

This instrument is administered to all participants that report a medical history of diabetes and data is recorded on the Diabetes Questionnaire (DQF) form. Participants who have diabetes are asked questions about their diabetes management, preventive care practices applicable to diabetes, and foot and eye care.

18.14 Food Security Questionnaire

Data on food security is collected on the Food Security Questionnaire (FSQ) using the U.S. Household Food Security Survey Module, a six-item short form developed by the National Center for Health Statistics to assess household food insecurity (i.e., lacking access to food for a healthy and active life) (Blumberg et al., 1999).

Citation:
Blumberg, S. J., Bialostosky, K., Hamilton, W. L., & Briefel, R. R. (1999). The effectiveness of a short form of the Household Food Security Scale. *American Journal of Public Health*, *89*(8), 1231-1234.

18.15 Life Space Questionnaire

The life space questionnaire (LSQ) is used to measure the extent of mobility and the range of places in which the participant engages in activities within a designated space and timeframe. Participants will provide responses about distance and frequency of activity with or without assistance (McCrone et al., 2019; Peel et al., 2005; Stalvey et al., 1999).

Citations:

Peel, C., Baker, P. S., Roth, D. L., Brown, C. J., Bodner, E. V., & Allman, R. M. (2005). Assessing mobility in older adults: the UAB Study of Aging Life-Space Assessment. *Physical Therapy*, 85(10), 1008-1019.

McCrone, A., Smith, A., Hooper, J., Parker, R. A., & Peters, A. (2019). The life-space assessment measure of functional mobility has utility in community-based physical therapist practice in the United Kingdom. *Physical Therapy*, 99(12), 1719-1731.

Stalvey, B. T., Owsley, C., Sloane, M. E., & Ball, K. (1999). The life space questionnaire: a measure of the extent of mobility of older adults. *Journal of Applied Gerontology*, 18(4), 460-478.

18.16 Neurological History

Neurological history (NHX) is a 16-item assessment to determine whether a participant has a nervous system disorder and the type of treatments administered, if applicable.

18.17 Physical Ability

Physical ability questionnaire (PAQ) is assessed using a 26-item questionnaire. Participants will provide responses to the level of difficulty with performing activities due to health or physical reason. Questions from the Atherosclerosis Risk in Communities Study Physical Ability Questionnaire (version 4) (# 1, 2, 3, 4, 5, 6, 7, 8, 9, 18, 19, 20), the Cardiovascular Health Study 6-month follow-up calls (#10, 11, 12, 13, 14, 15, 16), and the Jackson Heart Study annual follow-up calls (#23, 24, 25, 26) were used. Additional questions included question 17 “Taking medications?” because it is commonly included in the list of instrumental activities of daily living and questions 21 “Do you drive during the day?” and 22 “Do you drive at night” because driving is a critical part of life space mobility.

18.18 Quality of Life

Quality of Life (QOL) questionnaire consists of 12 questions (SF-12) about the physical and emotional health of the participant. Data is collected to assess how the participants feel and how well the participant is able to do usual activities (Ware et al., 2008).

Citation: Ware, J. E., Kosinski, M., Bjorner, J. B., Turner-Bowker, D. M., Gandek, B., & Maruish, M. E. (2008). sf-36v2 health survey: Administration guide for clinical trial Investigators. *Lincoln, RI: Quality Metric Incorporated*, 1-34.

18.19 Respiratory Symptoms

The Respiratory Symptoms (RSQ) questionnaire consists of 5 questions to assess whether a participant has difficulty breathing during physical activity (Fletcher et al., 1959).

Citation: Fletcher, C. M., Elmes, P. C., Fairbairn, A. S., & Wood, C. H. (1959). Significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *British Medical Journal*, 2(5147), 257.

18.20 Health Literacy

The Health Literacy (LIT) form consists of 4 questions to assess how well participants are able to understand information obtain from their doctors about their health (Anderson et al., 2021; Chew et al., 2004; Woloshin et al., 2005).

Citations:

Anderson, M. D., Merkin, S. S., Everson-Rose, S. A., Widome, R., Seeman, T., Magnani, J. W., ... & Lutsey, P. L. (2021). Health literacy within a diverse community-based cohort: the Multi-Ethnic Study of Atherosclerosis. *Journal of Immigrant and Minority Health*, *23*, 659-667.

Chew, L. D., Bradley, K. A., & Boyko, E. J. (2004). Brief questions to identify patients with inadequate health literacy. *Family Medicine,* 36(8),588-94.

Woloshin, S., Schwartz, L. M., & Welch, H. G. (2005). Patients and medical statistics: Interest, confidence, and ability. *Journal of General Internal Medicine*, *20*(11), 996-1000.

18.21 Perceived Social Environment

The Perceived Social Environment (PSE) form is used to ascertained participants' perceptions about their neighborhood cohesion, safety, and other neighborhood characteristics (e.g., noise, traffic, cleanness, recreation, walkability, access to food/shops).

Citations:

Mujahid, M. S., Diez Roux, A. V., Morenoff, J. D., & Raghunathan, T. (2007). Assessing the measurement properties of neighborhood scales: from psychometrics to ecometrics. *American Journal of Epidemiology*, *165*(8), 858-867.

Barber, S., Hickson, D. A., Wang, X., Sims, M., Nelson, C., & Diez-Roux, A. V. (2016). Neighborhood disadvantage, poor social conditions, and cardiovascular disease incidence among African American adults in the Jackson Heart Study. *American Journal of Public Health*, *106*(12), 2219-2226.

Hirsch, J. A., Grunwald, H. E., Miles, K. L., & Michael, Y. L. (2021). Development of an instrument to measure perceived gentrification for health research: perceptions about changes in environments and residents (PACER). *SSM-population Health*, *15*, 100900.

18.22 Bleeding History

The Bleeding History (BHX) form collects data on individual and family history of bleeding disorders, bleeding problems/complications during dental procedures, surgeries, or childbirth. Treatments and interventions for bleeding problems are also collected.

19 EXAM VISIT REVIEW AND EXIT INTERVIEW

Since the participant's safety is of paramount concern, data collected during the exam that could indicate the need for referral for medical care are reviewed with the participant prior to the completion of the exam and during the exit interview unless the alert condition required stopping the examination. An additional purpose of the exit interview is to verify that all components of the examination have been completed, to solicit comments and feedback 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 their provider of care that the results originate from a research study and cannot be equated to a clinical evaluation.

19.1 Data Inventory

The data inventory step is done after all interviews and examination procedures have been completed. A staff person reviews the participant checklist to determine that all interviews and procedures have been completed and checks participants' charts. After completion of the exam components is verified, participants are invited to change back into their regular clothes while the results of the exam are being prepared for review with the participants.

19.2 Exit Interview

At the end of the visit, exam results are reviewed with the participants by trained staff and a summary of study results for anthropometry, body composition and sitting blood pressure are provided to the participants. Participants are reminded that they should take their results to their health care provider and are provided with a duplicate copy for that purpose. The medications are also returned to the participants at this time.

The participant feedback form (PFF) form is completed to ascertain participant's global perspective of the visit. It is intended to provide participants with the opportunity to express any concerns or issues they may have had with the visit and provides input into their overall satisfaction with the procedures and approaches used in the field center, including staff encounters and information received.

20 QUALITY ASSURANCE

20.1 Staff Training and Certification

Staff training includes an overview of the Exam 4 components; an overview of epidemiological cohort research methods; instructions in research interviewing techniques; communication; respecting cultural diversity; and forms completion. Key components include:

- A thorough review of the data collection forms, instructions, and study protocol;
- Practice in the use of a non-judgmental attitude or response;
- Practice with the degree and nature of prompting permitted to deal with problem interview situations;
- Use of response cards;
- Practice handling participants' comments and recording relevant information on the note logs; and
- Practice performing procedures.

Certification and re-certification criteria for all elements of Exam 4 interviews and procedures are detailed in **Manual 12 Quality Assurance and Quality Control**.

20.2 Quality Control Monitoring

With participant approval, a sample of interviewer-administered forms are taped for review. Routine quality control is done through direct observation by the Field Center manager and data quality is monitored by the Quality Control Subcommittee.

21 ALERT NOTIFICATIONS AND RESULTS REPORTING

Alert notifications and results reporting are tracked using the Results and Alert Report (RAR) form. Participants and their health care providers, if applicable, are notified of alerts at the time of identification. Some alerts may be identified during the exam (e.g., blood pressure) and others may occur after the exam (e.g., brain MRI, Zio Patch, lab values).

Study results are reported to participants according to current guidelines. Laboratory tests and procedures 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.

21.1 Routinely Reported Results

When study results are received from the central laboratory and reading centers, they are combined into a summary report for dissemination to participants and their health care provider, if applicable.

21.2 Results Reported by Request Only

All other study measurements, *i.e.*, those not routinely reported to participants or their health care provider, are considered to be of research value only. If a participant requests them in writing, these results are provided on a case-by-case basis.

On the rare occasion that a request for a participant's study results comes from a third-party medical care payer, a results report can be released according to the following steps:

1. A signed statement from the participant authorizing the release of data to anyone other than the participant or their identified health care provider is required. A copy of the request and the authorization for release of study data is kept in the participant's chart.
2. The report contains only the information that was released to the participant's health care provider (or the participant), i.e., an exact copy of the cover letter and the results report.
3. The information is sent directly to the third-party with an exact copy to the study participant, and documented in the participant's chart.

22 PARTICIPANT SAFETY

Specific measures are taken in the design and conduct of the exam for participant safety. These include the use of a safety screener, operating procedures for handling potential emergencies, and alert and referral criteria.

22.1 Participant Safety Screening

At the time a participant's exam visit is scheduled, the Participant Safety Form (PSA) is used to ascertain and record conditions or circumstances that may convey risk in the course of the exam or that may result in exclusions from a test or measurement. Medical conditions, food allergies, or dietary restrictions are also ascertained.

The PSA form must be completed before a participant can proceed with the exam. The form is completed in REDCap and is included on the exam checklist. The PSA serves as the summary record of safety information. Thus, if the study participant or a staff person needs to update safety information provided previously, this is done by (a) changing the pertinent response on the PSA, and (b) adding a note log to that item with a brief explanation for this action and the staff person's ID.

22.2 Measures to Protect the Participant

Procedures with potential, although small, risk to participants include measurement of bioimpedance and physical function. Precautions are taken to minimize the risk associated with these procedures, including verification of a safety exclusion (see Section 22.3). Staff may re-ask the pertinent safety exclusion question, and may confirm with the study participant an exclusionary condition noted on the PSA (as Yes). If the condition is deemed to have been recorded in error, the staff may override

the previously recorded response/exclusion if authorized to do so. Otherwise, the staff asks for input of a supervisor.

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 **Manual 9** Specimen Collection and Processing.

Occasionally, bleeding persists after venipuncture, in which case procedures described in Manual 9 Specimen Collection and Processing are followed. The possibility of hypoglycemia with an 8-hour fast is diminished by routine inquiry during the scheduling of the exam visit about reasons which should exempt the participant from fasting. Methods for handling major and minor emergencies are described in **Section 23**.

For persons with conditions which require emergency and immediate referrals, such as cardiac events, angina pain, or blood pressures $\geq$ 200/120 mm Hg, the local cardiologist is consulted immediately, the exam visit is terminated as soon as the condition is observed, and another appointment rescheduled if appropriate.

22.3 Safety Exclusions from Study Procedures

1. Exclusion from any study component
   - SBP ≥ 200 or DBP ≥ 120 mm Hg (stop exam visit, arrange for urgent care)

2. Exclusion from bioimpedance estimation
   - Cardiac pacemakers (or automatic implanted cardiac defibrillator (AICD), if in doubt)

3. Exclusions from the two-minute walk
   - Inability to complete the 4-meter walk without a walking aid
   - Resting heart rate of 100 beats per minute or greater
   - SBP > 180 mm Hg
   - Cast or other immobilizing device on a leg

4. Exclusions from ankle-brachial index
   - Open wounds, ports, or dialysis shunts in ankle or arm cuff area;
   - Bilateral amputation;
   - Unable to lie down at <45° angle; or
   - Double mastectomy.

5. Exclusions from brain MRI
   - Cardiac pacemaker or defibrillator;
   - Starr-Edwards artificial heart valve; ARDS heart valve or a defibrillator;
   - Any metal in or near head, spinal cord, eyes, or chest;
   - Any internal electrical devices, such as cochlear implant, TENS stimulator (for pain),

vagal nerve stimulator, brain stimulator, gastric pacemaker, bladder stimulator, or any implanted mechanical pump (such as an insulin pump or pain pump);
- Permanent eyeliner;
- Surgery for an aneurysm;
- Surgically implanted dentures that use magnets; or
- Told by a physician they should not have an MRI exam.

6. Exclusions from Zio Patch

- History of allergy to skin adhesives;
- Implanted electronic device, including nerve stimulator, cochlear implant, or infusion pump. Note: pacemakers or defibrillators are not contraindicated for heart monitoring;
- Job where they may be exposed to a large magnetic field. Examples of jobs with exposures to strong magnetic fields including MRI imaging technician, electrician, and welder;
- Plan to undergo external cardioversion in the next 14 days; or
- Unwilling to shave upper left chest.

23 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 before departing the Field Center. In addition, there are minor emergencies (e.g., hypotension, fainting) that should be addressed on the premises. Although most emergencies are of the less severe nature, staff must be prepared for both types.

23.1 Major Emergencies

In a serious event, the primary concern of the staff is to address the participant's safety and implement pre-established procedures to get the participant to the nearest medical facility. The Jackson Medical Mall is located within 2 miles of the University of Mississippi Medical Center, which is a Level 1 Trauma Center. Needed life support procedures are continued until emergency care arrives or the participant is transported to a hospital. The specific emergency procedures define:

- Who is in charge during the emergency;
- Who is to administer treatments;
- Who is to be notified;
- What action staff is to take; and
- Which reports are to be filed.

The field center is required to have access to either a physician or a registered nurse at all times during which participants are interviewed and examined. The field center has the phone numbers of police and fire stations; ambulance services; and specific phone numbers or codes to alert medical teams, if applicable, posted in conspicuous places (e.g., reception area) in addition to trained

personnel and emergency equipment.

In each participant's record, the name and phone number of their physician or usual source of health care and the home and work telephone numbers of one or more contact persons should be available. The response to emergency situations is coordinated by the Field Center manager. The designated physician on call will be contacted; however, in no case is an emergency referral or care to be deferred while staff is attempting to locate the designated physician.

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

23.2 Minor Emergencies

The most common minor emergency is simple syncope (fainting) and near syncope. These events may occur during venipuncture.

Many syncopal episodes can be prevented if staff is alert to early signs. In any situation in which syncope is likely (e.g., after the venipuncture or standing up after supine exam procedure), staff should stand close to the participant and verify that they do not look or feel faint. If the participant looks faint or feels faint in the venipuncture area, the staff member should:

- Have the person remain in the chair and sit with their head between the knees or recline if the appropriate chair is available;
- Crush an ampule of smelling salts and wave it under the participant's nose for a few seconds;
- Provide the participant with a basin and a towel if they feel nauseous;
- Have the participant stay in the chair until they feel better and color returns;
- If the participant continues to feel sick, recline the chair, place a cold wet towel on the back of their neck, and notify the supervisor.

If a participant faints, they should be cautiously lowered to the supine position on the floor and one attendant immediately calls for a supervisor to assist the patient. The remaining attendant palpates for a carotid pulse and checks to be sure the participant is breathing then raises their legs above the plane of the body to increase venous return. If the participant has no pulse, staff should start cardiopulmonary resuscitation (CPR) and activate emergency procedures.

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, 8 oz of orange juice should be given immediately and the Field Center manager notified as soon as possible. If a hypoglycemic reaction has occurred, the person is evaluated by staff prior to leaving the premises.

A severe hypoglycemic reaction is 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 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, and Emergency Medical System should be activated

23.3 Emergency Equipment

A basic first aid kit is maintained in the Research Exam Center. The kit contains a reference guide of its contents, and is checked every year and immediately after each use. The Field Center Manager identifies a person responsible for the maintenance of the first aid kit.

23.4 Stopping Rules for Procedures and Interviews

Participant Safety/Alert Thresholds on Study Measurements

If a participant feels unwell or if an alert value is met on a study measurement the participant is referred to health care and the remainder of the field center examination may be deferred, according to the action levels specified. If the health care referral is an alert value or if the examination is discontinued, field center personnel explain the urgent need to seek medical care and assist the participant in making an appointment if this is helpful. The study participant is also told that JHS personnel will contact them within 48 hours as a courtesy follow up. During this follow-up call, field center personnel confirm that the participant has seen a doctor or has understood the need to seek medical care.

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 workstation. 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 exam. Participants unable to complete the full exam are invited to participate in the exit review and reschedule the clinic exam on another day.

Mental Health Emergency Procedures

In the course of the 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, 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 JHS, procedures are in place 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. JHS has personnel trained to respond to physical and medical emergencies and certified according to 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 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.

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 Field Center manager is notified of any suspicion of intoxication. The staff will explain to the participant why they will be excluded from the procedures and why they should leave the research premises (i.e., that they appear to be intoxicated, smell like alcohol, is staggering). To protect the participant from possible injury, staff must make sure that the client does not drive home, either by calling a taxi or calling the police to escort them home. Intoxication must be documented as an incident report.

24 PROCEDURES TO REPORT ADVERSE EVENTS (AE) AND UNANTICIPATED PROBLEMS (UP)

As NIH-supported research that involves human subjects, the study protocol includes procedures for

identifying, monitoring, and reporting all adverse events (AEs, both serious and non-serious 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).

Per OHRP guidelines, an AE is an adverse change in health or unfavorable medical occurrence that occurs in a person who participates in the study, which may or may not be caused by participation in the study. An AE includes 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 the study, its tests and examination procedures do not by themselves constitute an adverse event. An AE and problems that are not foreseen or mentioned in the study protocol or the informed consent are considered unanticipated. If an UP suggests that the research places the participant at increased risk (as defined below), the UP must be reported to the University of Mississippi Medical Center Institutional Review Board (IRB), and to the NHLBI as described below.

An AE and UP must be addressed promptly according to institutional safety guidelines to quickly resolve any safety concerns or participant discomfort.

24.1 Definition and Classification of AE

Serious AE
A serious AE occurs if it affected a pregnant study participant, a fetus or a newborn, or results in any of the following outcomes:

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

Unexpected AE
An unexpected AE occurs 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.

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 the study.

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 determination often requires an assessment of how likely an AE is related to participation in the study, 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 are not related to the research procedures or the setting of the research.

24.2 Definition and Classification of UP

The OHRP considers an UP to include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected;
- Related or possibly related to participation in the research; and
- 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 majority of adverse events are unanticipated. UPs can include unforeseen incidents, experiences or outcomes; if they also are related or possibly related to participation in the study and indicate that they place the study participant or others at a greater risk of harm they qualify as a UP.
- All serious AEs are considered to be unanticipated and unexpected, whether they are study-related, possibly study-related, or not study-related. In contrast, not all UPs are serious AEs.

24.3 Reporting of AE, UP, and Information Flow

If a participant experiences an AE or UP, the first priority is to attend to the participant's safety. While a staff person always remains with the participant, the licensed clinical staff member 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 the IRB's guidelines, and all AEs and UPs are promptly recorded on the Adverse Events Unanticipated Problems Log (AEL). A Serious Adverse Event/Unanticipated Problem Form (SAE) must be completed for all serious adverse events and unanticipated problems.

Each time a SAE form is entered in REDCap, the JHS staff person completing this task should promptly notify the Coordinating Center by email that a SAE form has been entered. The AEL and SAE forms are reviewed by the Coordinating Center and a report of the event to the NHLBI according to

schedules shown in **Table 6**. No direct notification of an AE or UP to NHLBI is required. AEs 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 is presented below.

Table 6

Unanticipated Problems and Types of Adverse Events, Required Actions and Timing

	Research Exam Center			**CC**	**Exam Operations Subcommittee**	**Steering Committee**
Response	Address any safety issues; notify clinical staff	Record in REDCap; notify CC	Report to IRB	Notify NHLBI	Review study procedures; propose revisions if warranted	Review study procedures; modify protocol if required
Unanticipated Problems	Immediate	Within 48 hours	Continuing Review	Within 7 days	Within 14 days	Within 30 days
Serious Adverse Events	Immediate	Within 48 hours	Within 10 days	Within 7 days	Within 14 days	Within 30 days
Non-serious Adverse Event	Immediate	Within 48 hours	Within 10 days	Quarterly	Within 30 days	Quarterly
Anticipated Problem, not an AE	Immediate	N/A	N/A	N/A	N/A	N/A

25 APPENDIX

Appendix 1. Summary of Observation and Equipment Checklists

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

Date:

Quarterly reporting period:

A. Observation Checklist

	Technician ID	Supervisor ID	Date (mm/dd/yy)
General interview			
Medical interview			
Food frequency questionnaire			
Informant interview			
Neurocognitive assessments			
Anthropometry			
Sitting blood pressure			
Biospecimen collection			
Physical function			

B. Equipment Checklist

	Frequency	No. times assessed	No. times within calibration
Anthropometry			
1) Tanita scale read zero	Daily		
2) Balance beam read zero	Daily		
3) Wheelchair scale read zero	Daily		
4) Tanita scale calibrated	Weekly		
5) Balance beam calibrated	Weekly		
6) Wheelchair scale calibrated	Weekly		
7) Tanita scale professional calibrated	Annually		
Blood Pressure			
1) Checks for the OMRON BP machine	Quarterly		
Physical Function			
1) Grip strength dynamometer	Semi-Annually		
Biospecimen collection			
1) Refrigerators, freezers, room temp	Daily		
2) Speed of centrifuge	Annually		
3) Calibration and professional cleaning of pipettes	Annually		
Echo machine	Quarterly		
ECG machine	Quarterly		
Ziopatch	Quarterly		
PWV			
1) Maintenance Procedure (submit Maintenance Sheet to CC with this checklist)	Monthly		

Comments:

Appendix 2. Anthropometry Equipment Calibration Log

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

Week of [Monday's Date]: Field Center: Tech ID:

Daily Checks

Scales read zero ___ M ___ T ___ W ___ Th ___ F ___ Sa ___ Su

Weekly Checks

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

Date service REQUESTED:

Date RECALIBRATED by service technician:

B. Repeat calibration because of moving scales Date: Reading:

Date: Reading:

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