FRAMINGHAM HEART STUDY

OFFSPRING EXAM 10
OMNI EXAM 5

RESEARCH CENTER/OFFSITE PROTOCOL MANUAL

10/01/2019 – 08/31/2021

Gen 2 Exam 10 Omni 5 Components

Section I: Informed Consent & Tracking Procedures

1) Informed Consent
2) Waiver of Informed Consent
3) HIPPA - Release of Health Information for Research Purposes
4) Tracking Information Form
5) Short/Split Exam Procedures

Section II: Clinical Measurements & Procedures

1) **Lab**
   a. Blood
   b. Urine
2) **Anthropometrics**
   a. Weight
   b. Height
   c. Waist Girth
   d. Hip
3) **ECG**
4) **Observed Physical Performance**
   a. Hand Grip Test
   b. Walk Test

Section III: Tech-Administered Questionnaires

1) **Cognitive Function**
   a. MMSE
2) **Physical Function**
   a. KATZ-ADL Scale
   b. Rosow-Breslau
   c. NAGI
3) **Depressive Symptoms**
   a. CES-D
4) **Physical Activity Questionnaire**
   a. Exercise
5) **Other**
   a. Fractures
   b. Proxy Form

Section IV: Physician-Administered Medical History and Physical Exam

1) Medical History
2) Resting Blood Pressure

Section V: Self-Administered Questionnaires

1) Socio-demographics
2) SF12 Health Survey
3) Sleep Questionnaire
4) Bleeding
5) Pain Assessment
6) Willett Food Frequency Questionnaire

Section VI: Non-Invasive Vascular Testing

1) Tonometry (Arterial Pressure Waveform Test)

Section VII: Exam Completeness

1) Referral Tracking & Adverse Events
2) Exit Interview

Section VIII: Ancillary Studies

1) Capsite Pain Assessment
2) Fibroscan
3) Platelet Study

Equipment For Gen 2 Exam 10 Omni 5 Procedures

1. A. Research Center: Detecto Scale (3)
Worcester Scale Co., Inc.
Higgins Industrial Park
228 Brooks Street
Worcester, MA 01606
(508) 853-2886
www.detectoscale.com

B. Offsite: SECA Portable Scale Model #841
MSI: Measurement Specialties Inc.
Fairfield, NJ 07007

2. Weight to calibrate scale: 50 lbs.
Worcester Scale Co., Inc. (See above)

3. SECA Stadiometer (3)
Halliday Medical
4-694-581
Walpole, MA 02081
[redacted]

4. ECG Machines: GE MAC5500 (4)
GEHealthCare
8200 West Tower Avenue
Milwaukee, WI 53223

[redacted]

[redacted]

5. Portable standard mercury column sphygmomanometer (6)
Baumanometer, 300 model; Catalogue #0661-0320

[redacted]

http://www.wabaum.com
[redacted]

6. Aneroid Sphygmomanometer – gauge type (offsite- 2)
   P/N 5090 – 03 Tycos
   Samuel Perkins, Inc.
   Quincy, MA 02169

   [redacted]

7. Bauman latex free blood pressure cuffs in four sizes: regular adult, large adult, pediatric, thigh.

8. Litman stethoscope tubing and earpieces with bell (4): Classic II

9. Tailor's plastic tape measure (3)

10. 60 Memory Stopwatch # 1025CC
    Control Company
    Heart Square (4)
11. Pocket Talker Pro (2)

12. JAMAR dynamometer (3)

Equipment Calibration Time Table

Activity	Daily	Weekly	Monthly	Yearly
Detecto Scale				
Zero Reading	**X**			
50# Weight			**X**	
Professionally Calibrated				**X**
Manometer				
Zero Reading	**X**			
Check Inflation System			**X**	
Stadiometer				
Check Level- with Calibration Tape			**X**	
Tape Measure				
Against Calibration Tape			**X**	
Dynamometer				
Zero Reading	**X**			
Professional Calibration				**X**
Stopwatches				
Professional Calibration				**X**

Framingham Heart Study

Manual of Procedures

SOP-version 1.0

August 23, 2019

Maureen Valentino

Recruitment Manual

Second Generation & Omni 1

Exam 10/5 October 2019- March 2021

Tracking of Revisions to this FHS Protocol SOP

Revised Section	Revision Author	Date (s) of Revisions; source	Approved by, Date	Revisions	Previous Pages #s section changed	Distribution Date
Scheduling	MV	8/23/2019				
Admitting	MV	8/23/2019				

Table of Contents

1.0 Exam Overview

Gen 2 Exam 10/Omni 5 recruitment for the Second Generation and Omni 1 begins in October 2019 and ends in March 2021. The projected recruitment is 1800 from 2 cohorts. There will be 4-5 participants scheduled per day, Monday through Friday, for a total of 30 participants each week. It is anticipated that the exam will need 3 Saturday exam dates each spring and fall of the cycle to accommodate the needs of the participants.

Calling for exam appointments is done by anniversary date of the previous exam. For example, participants who did not come in for Exam 9/4 would be first on the new Exam calling list, then it would move to those participants who came in at the beginning of last Exam. Participants who contact us from out-of-state and express that they will be in the area at a certain time will be accommodated regardless of exam date.

Once the recruitment begins, a participant is coded accordingly: Scheduled, had Exam10/5, Call back for Exam 10/5, or Refused Exam 10/5. The call-backs for Exam 10/5 are coded and generated as a separate calling list based on the new call-back date.

In February or March of each year, the Framingham Heart Study sends a newsletter to all the participants. This is an important recruitment tool and reminder for participants. In addition to listing the contact information for the participant coordinator, each newsletter announces the exam phase, i.e., the “start of the exam,” “the ongoing exam,” or “the exam is ending!” A postcard mailing is sent to anyone out of state in March/April to heighten the awareness of the exam (see postcard script). A final postcard mailing goes out approximately 6 months before the cycle closes to any participant who has not attended Exam 10/5.

2.0 Participant Tracking System (PTS) Components

(See Appendix XX)

Find a Participant
This screen contains multiple ways to find a participant. One or several fields may be filled in to narrow a search.

Booking
This screen lists all the appointments ever scheduled for the participant. Within this screen you will find specific information pertaining to the exam: date, name and number, exam site, special instructions (i.e., "came with sis"), how often they canceled/rescheduled, and who booked it.

Physicians
This screen lists the participant's primary care physicians.

Family
This indicates family members who are IN the study and linked to the participant.
Note: Not all family members that are in the study are linked in PTS at this time.

Roster
This is the primary resource for tracking participants and maintaining status information that is used for reports and grant applications. It is extremely important that information on the Roster is accurate. For this reason, in order to make changes on the Roster, users must have USER Training as well as their own user accounts. Permits must be requested through the Recruitment Supervisor to the Tracking Coordinator and the Database Administrator.

Referral (Formerly known as F14)
This screen contains a coded list of information about the participant, including whether or not they are alive, exam status for the most recent exam cycle, when to call back for an exam, etc. This is where confidential comments are listed and it also may contain contact information for a participant's additional contact.

Mailing
This screen documents a second address for the participant. This would be a second home or vacation home. The mail code status also resides in this screen.

Brain Donation
This screen indicates if the participant is participating in the Brain Donation Program.

Cell
This screen indicates if a cell line was collected on the participant.

Exams
This screen indicates the Exam number and date of Core exams only.

CT Tracking
This screen indicates participation in the Coronary Calcium CT study.

Proxy Tracking
This screen indicates the designated proxy and alternate for the participant.

Call Log
This screen indicates who at the Heart Study has contacted the participant, the reason for the contact, and the results of that contact.

Under Review Screen

Health Status Update Tracking
This screen indicates when the participant had Health Updates done, including how it was done (i.e. phone, paper, online), the tech ID (if administered by staff), and the tech ID of the keyer.

3.0 Scheduling a Participant

(See Appendix XX)

When scheduling a participant, upon entering their ID Type and ID number, the "Roster" screen will open up.

Roster: This screen is the face screen in PTS for each participant. Name, nickname, date of birth, address, and all contact information are located on this screen. This includes phone numbers, email address, and people to contact should the participant become unreachable. The Survival Date (last date known to be alive) and the Event Date (most recent health update or exam) are also on this screen. **Survival Status** and **Survival Date** should be checked first on the roster screen. This tells you if the participant is alive or deceased. Before calling the participant, review the **address field,** to be aware of a different time zone. At the bottom of the roster screen are also 3 fields (**Roster_contact_work; Roster_contact_email; Roster_contact_cell)** that indicate whether or not the participant has given permission to be contacted each way. **Consent status** and **consent date** are located toward the bottom of the roster screen. Although these fields are not always completed (only if the participant has gone through the neurology study), they are important as they can indicate if a participant has cognitive impairment.

Referral code: This number (shown on the Roster screen above Survival Date), indicates the status of the participant and is changeable only on the Referral screen. On the Referral screen, the drop down menu will indicate the meaning of each code. *It is extremely important to verify the referral code before calling the participant.*

Comment field: This screen often contains helpful information regarding the participant. Some examples of this are if the participant schedules with another family member, the best time to reach the participant, if they had multiple cancellations for the Core Exam, or need special accommodations. If "**F14**," "**See F14,**" or "**See Referral Screen**" is noted here, there is important information to be found on the Referral screen, and it must be checked before participant contact.

Referral Screen: This screen contains a coded list of information about the participant, including if they are alive, exam status for the most recent exam cycle, when to call back for an exam, etc. This is where confidential comments are listed and also may contain contact information for a participant's second contact.

Additional Screens

Booking Screen: This screen lists all the appointments ever scheduled for the participant. Within this screen you will find specific information pertaining to the exam: date, name and number, where done, special instructions (i.e., "came with sis"), how often they canceled/rescheduled, and who booked it. The previous appointment often gives pertinent information that occurred at that appointment, i.e. fainted @ blood draw, latex allergy, etc.

Family: This screen is helpful to identify how many family members are in the study and the relationship: spouse, children, parents, etc. Often family members may schedule an appointment together. It is helpful to screen the family member to be sure they have not already scheduled.

How to create an appointment in the Booking Screen

Once you and the participant have reached an agreement on a date and time, the following steps must be made in three PTS screens:

Roster Screen

Change the Survival Status to the date on which you speak with the participant to schedule the appointment.

Add date on Comment line in the roster screen: if it is the first appointment scheduled it should start with month/year you scheduled them and then the month/date of the scheduled appointment. Example: 5/17 scd 6/13 (in May 2017 they were scheduled for June 13, 2017)

Referral Screen

Change the Referral code to a (6) = Scheduled/Had Exam.

Booking screen

Create a new appointment by clicking on **New Record.** This creates a new appointment. Enter in the mandatory fields:

1) Date/time, exam, exam type, booker's initials.
2) Add additional comments as needed, i.e. LATE ADD, w/siblings etc.
3) If a participant is cancelling an appointment and cannot yet reschedule, change referral code on referral screen to (3) =call back and enter date that they would like to be contacted again in call back date field. If the participant does not provide call back date, always use the following month and the 1st as the date. In the Booking screen, change drop down from "current appointment" to "cancelled appointment."
4) If participant is rescheduling an appointment, change referral code back to (6) = scheduled/had exam on the Referral screen, and change drop down back to current appointment on Booking screen. On the comment line on the Roster screen, add the new date onto what is already noted. E.g. 5/17 "scd" 6/13cx "rsch" 7/15.

Marking a participant as a "Call Back"

If the participant is contacted but is unable to schedule an appointment at that time then the status should become a **call back**. The recruiter should obtain a "call back" date from the participant, which will better suit the scheduling needs of the participant. This date can be a month away or a year away. The recruiter should set the call back date based on the time the participant wants to schedule. The schedule is usually completed a month in advance; if a participant states they will be available in June – the call back date should be for 5/1. The 1st or the 15th are the only dates that are used. This is done to keep order to the call back list.

1) Change survival date to date of contact.
2) In the Referral screen, change referral code to a (3) =call back.
3) In the call back date indicate the date established by participant MM/DD/YYYY
4) Document any notes relevant to the conversation in the referral screen.
   Example: participant pregnant call back in 6 mo. The note should start with the m/yy
   As there may be other notes added or previous notations.

Scheduling a Saturday Appointment

If a participant schedules for a Saturday:

1) Change survival date to date of contact.
2) Add date on comment line in the roster screen: if it is the first appointment scheduled it should start with month/year you scheduled them and then the month/date of the scheduled appointment. Example 5/17 scd 6/13.
3) In the Referral screen, change referral code to a (67) =scheduled Saturday exam.
4) Create an appointment in the booking screen.

If a participant is a callback for a Saturday:

1) Change survival date to date of contact.
2) In the referral screen, change referral code to a (37) =callback Saturday exam.
3) In the call back date indicate the date established by participant MM/DD/YYYY
4) Document any notes relevant to the conversation in the referral screen.
   Example: participant pregnant call back in 6 mo. The note should start with the m/yy
   As there may be other notes added or previous notations.

Marking a participant as a "Refusal"

In cases where the participant says they will not be able to do the study this time, the recruiter should first be sure to describe the window or time frame for the exam. In most cases, the participant would prefer a call back rather than eliminating the opportunity to do the study all together. If they are a refusal for the exam, do the following:

1) Change survival date to date of contact
2) On the Referral screen, change referral code to a (2)=Refusal
3) On the Referral screen in the comment section, indicate M/YY and reason for refusal

Drop Out

If a participant says they wish to drop out of the study, the participant should be instructed that a coordinator will contact them to arrange the withdrawal.

Cognitive Impairment

Identifying potential cognitive impairment prior to scheduling.

1) Check comment line and/or referral screen.
   Comments regarding cognitive status can be documented in these two fields. For example if a diagnosis of dementia was indicated on an MHU, but the participant was never seen in FHS neurology, it would be noted here. This information should alert the recruiter to the potential of compromised cognitive status. Should the status be of concern, the recruiter should contact the identified research proxy and or a next of kin (LAR) for consult.
2) Consent Status field in PTS.
   The consent status and consent status date should be reviewed prior to calling a participant. If the participant has been seen in FHS Neurology or Neuropsychology studies, a consent status (a numeric key) will be indicated. The date the participant was seen to obtain that information will also be indicated. Both of these are important in knowing how to proceed. The numeric key is 1-5 (see appendix). The recruiter would still proceed with scheduling if the score is 3 or less, but depending on the date of consent status i.e. no cognitive testing for several years, should be aware of the potential for further cognitive decline.

If a participant has a consent status of 3 or 4 determined by Neuropsychology testers in the Consent Status, the participant's Research Proxy, LAR, Next of Kin should be contacted for scheduling.

Offsite Scheduling: Cognitive Impairment:

When scheduling an offsite exam, the same procedure should be used as is done when scheduling a research center exam. The recruiter should be checking the consent status, notes on the comment line and the referral screen for any indications of impairment.

If a greater degree of impairment is suspected, then the Research Proxy or LAR should be contacted. The exam should be described in detail to the designated representative and permission to see the participant established. Any concerns about components of the exam that might be of issue should be documented at the recruitment call to insure they are eliminated at the offsite visit. The proxy for the participant should always be asked if they would like to be present for the exam and their schedule accommodated.

If the research proxy or LAR does not wish to be present, the procedure to obtain consent from the proxy should be established prior to scheduling the exam.

If family members refuse the exam, ask if they are willing to do a telephone health history update.

Note: At the time of the appointment if the participant refuses to have the exam his or her objections will be honored.

Cognitive Impairment Identified at the Offsite Visit

In cases where the participant is scheduled for an offsite and at the scheduled visit impairment is determined, a Waiver should be instituted and the components of the exam allowed under a Waiver can be administered.

Note: At the time of the appointment if the participant refuses to have the exam his or her objections will be honored.

The recruitment department should be notified of suspected cognitive status for proper documentation in PTS and to determine if a Research Proxy or LAR should be notified.

4.0 Chart Preparation

OVERVIEW

1. Print Exam Schedules
2. Pull Participant Charts
3. Print Health Status Update Lists
4. Check Charts for Health Updates
5. Locate and copy Health Updates
6. Verify Weekly Exam Schedules with Participant Coordinator
7. Copy Consent for Pregnancy Test on pink paper & place in chart of female participants
8. File the prepared charts by day in Admitting Room cabinet

SCHEDULES

Weekly schedules will be closed on Wednesday by the participant coordinator for verification. An email will be sent when the list is finalized. At this point an email will be sent regarding any reschedules prior to Friday.

To print the weekly schedule on Friday, go to:

-- Crystal Reports/PTS/Recruiting
--Booking AM Report
--Print the schedule for each date separately
--Send to printer
--Use the refresh icon to do next day
--Use the home icon to return to PTS menu.

Highlight the day of the week and any comments or notes on list.

PULL CHARTS & HEALTH UPDATES

For each participant on the schedule, pull the chart from their last exam.

Sign-out card:

Out To:	Exam:
File Number or Name Out:	ID type & ID number:
Date:	Date of Exam:

Print Health Status Update list for each day & ID Type:

Crystal Reports/PTS/Admitting

Hsu.dates.rpt
Enter ID type and begin and end dates
Printer icon HP2
Use the refresh icon to change ID type
Repeat for each ID type

Check chart for the latest health update. If not in chart check the file cabinets opposite the supply closet (2nd flr) and in Room 212. Check with Tracking Review if you have any problems locating the current health update form.

Verify correct name and number and make copies of pages 1 & 5 for Exam 10/5 chart. Return original to current location.

EXAM 10/5 CHART

The Exam folder goes inside the old chart on top of the last exam.

Gen 2 = Teal

Omni 1 = Maroon

Except for the Admitting Form, all records on top of the last exam will be brought forward and filed in the Exam 10/5 folder.

All the MRI Reports, Cognitive/Stroke Clinic Reports and Examination 8/3 and 9/4 reports in the back of the last exam come forward to the back of the Exam 10/5 folder.

CHART ORDER

- Admitting Form
- Pink Consent for Pregnancy Test (if female participant)
- Summary of Findings
- Medical History Update Forms in reverse chronological order (Latest on top)
- Hospitalizations and Medical Records
- Medical Record Request Letters and Consents for Release of Information
- Brain MRI Reports in reverse chronological order
- Cognitive/Stroke Clinic Reports in reverse chronological order
- Exam 8/3 and 9/4 physician letters in date order

Bring Charts down to the Admitting Room and file in 2nd drawer of file cabinet.

File by day in numerical order by appointment time.

Put daily schedule list on top of first chart for that day.

5.0 Exam Preparation

CLOSING OUT A WEEK

At the point where a week has been fully scheduled, it is then considered "closed". An email is sent to the recruitment team and the appointment letter/chart prep staff. Any ancillary study coordinator who is actively recruiting should also be cc'd on this email. Any appointment added after a week is closed is considered a **LATE ADD.** A comment should be added to the appointment in the booking screen on the designated line. This allows the comment to be printed on the daily schedule insuring the "LATE ADD" is clear to all participating in the exam preparation process. After adding the participant to the daily schedule, an email should be sent to invested parties. The header in email reads **LATE ADD _/_/_** (date of late add), **appointment time,** and **INITIALS** of that participant.

FRIDAY

1) The appointment book is compared to the printed schedules for the following week. This review is done to insure the accuracy of the schedules and to insure all **LATE ADDs** have been processed.
2) Print copies of schedules by week.

EMAIL NOTIFICATION IS CRITICAL TO ABOVE STAFF AND CHART PREP STAFF

6.0 Admitting

Before admitting:
Once the computer or tablet/scanner is all set up: Open RedCap and admitting forms

1) Greet participant by name
2) Pull chart
3) Ask for paperwork and medicine bag
4) Put label on medicine bag and return to participant
5) Review back of appointment letter to be sure completed
6) Clip appointment letter and food frequency form to inside flap of chart (if no food frequency form, write on post-it and stick on chart cover)
7) Pull name tag (in chart and scan on BAR CODE STICKER), place cursor on Field=Enter a new or existing FHS –ID ask name and birthdate then **SCAN**
8) Participant Information Page should come up
    a) Date of this FHS exam, click on "today"
    b) Site, click on "Heart Study"
    c) Verify their first and last names
    d) Simultaneous to this, check name on the Admitting Form
    e) Click on save and go to next page
9) Research Proxy:
    a. Explain the purpose of the document to participant *(See Appendix XX)*
    b. Enter "resides at" address
    c. Collect info on primary and alternate proxies
    d. Drag document over to participant monitor & expand it
    e. Click "Today" for date
    f. Click "Add Signature" and have them sign
    g. Click "Save & continue"
    h. Go to top PDF icon and click on "PDF data"
    i. Click on "print and double side" under properties
    j. Print 2 copies (1 to participant, 1 to Recruiting)
    k. Click on "save" and continue to next form
10) Exam 3 Consent Form
    a) Ask if the participant has read the consent form and if *yes,* ask if the participant has questions; if *no*, give them the binder to read the consent form and upon completion of reading, ask if the participant has any questions.
    b) If the participant has read document, scroll down to check box page
    c) Drag document over to participant monitor & expand it
    d) Have the participant check the boxes with the mouse (observe to be sure they are checking all boxes). If any hesitation in checking boxes, engage the participant to address any concerns
    e) Click "Add Signature" and have them sign

The admitter should click on "Witness (2) Signature" and "Today" for the date. Print 2 copies (1 to participant, 1 to the chart) **Take the opportunity, while they're reading the consent, to cross check info on admitting form, i.e. physician, proxy names (almost always on the admitting form), spouse, contact, child, etc.**

11) Medical Records Release (currently in paper form)
    a. Put an X at the signature and date lines
    b. Give to participant and ask them to read it over
    c. They then sign and date it
    d. Make 1 copy for the participant; the original goes in the chart.
12) Pregnancy Determination Form (pink paper)

    Ask all questions and check the appropriate box. Circle menopause if female has gone through menopause.
13) Admitting Form

Prior to administering admitting form explain to the participant that this information is being collected for the purpose of tracking the participant. Should we lose contact with the subject, this information will be the resource for locating the participant.

Cognitive Impairment

Procedure for obtaining of consent:

The exam appointment will be arranged by the designated Research Proxy and/or another responsible party (i.e. LAR,). The Research Proxy or LAR (spouse, next of kin) will be informed of the content of the exam and asked to provide written consent. The ideal proxy for the participant would be the Research Proxy designated by the participant at Exam 9/4. This information would be in PTS under proxy field.

If there is no designated research proxy, then consent should be obtained by a Next of Kin (i.e. spouse, child, niece, nephew, etc.). Should the research proxy, family member/responsible party object to a Heart Study visit the recruitment attempt should be terminated.

If there is no Research Proxy in place or available next of kin – Waiver of consent can be implemented. Only designated testing permitted under Waiver of Consent

If consent is provided by anyone other than the participant, the proxy is encouraged to be present at the exam appointment.

The following script should be used when placing the call to the participant's family members:

Hello, this is _____ (staff name) from the Framingham Heart Study. I am calling to let you know that we will be arranging an appointment to visit with your mother/father/relative for his/her 10th Heart Study exam. As you may know, your mother/father/relative has been participating in the Heart Study over the past 50 years. The current exam includes questions regarding his/her medical history since his/her last exam, ---------- (add a nursing home chart review if applicable). The exam will not involve any invasive testing or blood samples (if offsite). I'd like to visit

with _____ (participant name) on _____ (date). Would you like to be present at the exam?

If they want to be present, but cannot meet when suggested, arrange a date and time that works for them.

If they do not want to be present, verify contact information and instructions for mailing a consent form.

If family members refuse the exam, ask if they are willing to do a telephone health history update.

Note: At the time of the appointment if the participant refuses to have the exam his or her objections will be honored.

Cognitive Impairment Determined in Admitting or In Exam

If cognitive impairment is determined at the time of the exam, waiver of consent is implemented. This would usually be identified in the admitting station.
The consent still may be administered. The research center staff should be notified immediately. The research center protocol may be implemented. The admitter should contact recruitment to initiate consent by a research proxy or LAR.

If a question of cognitive impairment occurs after the admitting station, the research center protocol should be implemented and recruitment contacted to attempt contact with a research proxy or LAR.

It is important to note any document administered at the time of the exam; consent, research proxy or medical release, is invalid if a participant is determined to be cognitively impaired. **This does not invalidate previously administered documents.**

7.0 Post Exam Chart/Reports

Receiving charts (daily)

Put all received charts in drawer labeled "Charts Received from RC", separate by date using daily sheet.

Before putting charts in the drawer, check them in:

1. Check off day's charts using the daily sheet – put a physical check mark and write "rec'd"
    a. Make sure all charts are rec'd for that day
    b. If any chart is missing, investigate – check with Research Center staff to locate
2. Move the ECG forward to the front of the chart
3. Write date on chart cover with sharpie – make sure the date is placed on the long outer chart folder edge and is visible (not covered by prior Research Center Exam tab)
4. Put the days' worth of charts in file drawers in date order
5. Do not put charts in drawer unless they are checked in

Post exam results

When you receive Exam results (making sure results are in date order) file them in each participant chart in front of the ECG

1. The results – such as ECG cards, labs, etc. – will be received at different times. Keep them in the results caddy until you have time to file; always order the results by date.
2. File the results in the chart. You will need two copies of each report to be mailed – one to mail out and one to keep as a record in the chart of what was mailed.
3. Post exam reports to file and mail:
    a. To the participant's MD
        i. MD letter with any findings that require follow-up with participant's healthcare provider
        ii. Routine labs
        iii. Copy of ECG
    b. To Participant
        i. Participant Letter with any findings that require follow-up with healthcare provider
        ii. Routine labs
        iii. Cardiopulmonary fitness evaluation result letter (Ancillary Study)
        iv. ECG card

***General Comment**: Copies need to be made of all correspondences – results and letters*

Mailing

1. If missing any post exam result item, confirm that the item is truly missing. In the Research Center for example, if there are no labs, then confirm that no labs were done – use master lab sheet from the lab, etc. to verify this.
2. Convention regarding mailing letters:
    a. On File copy of letter at bottom write in pencil the date mailed and by whom (initialed). If nothing special is noted, assume standard packets were mailed as listed above in 3a. If something was missing or only a partial mailing was done for some reason, then list

what was sent, the send date, and initials. If future items are then sent, due to some reason (for example a medically actionable result), write at the bottom of MD letter the item sent plus "sent, date, initials".

b. We assume the standard MD and participant packets were mailed if we see "sent, date, initials" on MD letter. Anything non-routine should be clearly itemized, dated, and initialed at the bottom of the MD letter. It is OK to write "sent, date, initials" on any item within the chart as well (but not required). The general idea is that when the chart is picked up in the future, anyone should be able to find documentation of what was sent and when by looking at the bottom of the MD letter and on other notes left on the chart.
c. Convention: Participant packet and MD packet <u>are always mailed on the same date</u>
d. Before mailing, confirm that participant name and FHS ID (as it appears) are on each mailed item.
e. Before mailing, confirm MD name/address and PPT name/address against Admitting form

3. After mailing, check off the daily sheet saying "mailed/initial" so you are sure post exam reports for all participants have been mailed

Refile Chart **

Reorder the chart as follows:

1. Tracking Info (Research Center Exam 10/5 Admit Form)
2. Summary of Findings (yellow)
3. Lab results (Participant & MD)
4. Lab Test Request
5. Fibro Scan Letters (if applies)
6. Participant Result Letter
7. Appointment Letter
8. Medical Records (Reverse Date Order)
9. Medical Records Request Letters (Authorization)
10. Health Updates (Reverse Chronological Order); recent on top
11. Research Center Exam Consent Forms
12. Research Center Exam 10/5 ECG
13. FHS Brain MRI Reports (Reverse Date Order)
14. Stroke, Dementia, Cognitive Exam Summaries (Reverse Date Order)
15. Research Center Exam Physician Letters (Date Order)

*** Refile the chart in the medical record file room.*

Expedites (urgent post exam report)

1. Protocol for expedited charts
    a. Expedites – flagged in Research Center
    b. Coordinator sends out email requesting lab and CPFE reports
    c. FHS Physician/NP reviews chart
    d. Generate MD/Participant letter as described above and mail

8.0 Death/Condolence Letters

The Recruitment team is responsible for sending out condolence letters to the families of participants who have died. The team learns of deaths either through a Death Information Form or the Weekly Obituary Log. *(See Appendix XX)*

When you receive notification via a Death Form, go to the Roster screen and on the "comment line" enter "DECEASED" and the date of death and how you learned of the death (obituary, call from family member, etc.). Then go to the Referral Screen and change the code to Deceased (5).

When you receive notification from the Weekly Obituary Log, go to the Roster Screen and change the Survival Date to the date of death on the log, and the Survival Status to 1=Dead. (When a death appears on a weekly or monthly log, it means it has been verified by Medical Records.)

Each week the team receives a report on who was reported as dead. (It does not mean the participant died that week; the participant may have died a year ago, but it is that week when the Heart Study learned of the death.) At the beginning of the month, the team receives a Monthly Report for the previous month.
After the first week of the month, compare the weekly and monthly reports for the previous month, making sure that all the names on each weekly report appear on the monthly report.

Determining who receives the Condolence Letter
Go into PTS and open up the deceased participant's Roster screen. Verify that the Survival Status says 1=Dead. Look for a spouse/partner. If the spouse/partner is alive, that is the person who receives the letter. *The letter is addressed to Mr. /Mrs. First and Last name of spouse.*

If there is no spouse/partner, look at the address screen to see if the participant was living with a family member. If not, look in the Contact information to see if a child is listed. **If a child is listed as a contact and is in the study, verify the child's address by going into the child's own PTS screen.** If no family member is listed as a contact, look on the Family screen to see if the deceased participant has any children in the study. If you are confident you have good information for the child, then they receive the letter. If there is no spouse or child listed, look in the Contact information to see if there is another family member listed—sibling, cousin, etc. If there is and an address is given, that person will receive the letter. Sometimes the contact is also in the Heart Study. If so, go to that person's Roster screen to verify that you have the most current information. *The letter is addressed: To the Family of [Participant's Name,] c/o Family Member's Name, Family Member's address.*

You can also look at the Death Information Form (if there is one) to see how FHS found out about the death. Sometimes family members are listed there and they can receive the letter.

You can also search for a newspaper obituary to see who is listed as next of kin.

If you can find no family member who could receive the letter, a letter can be addressed: *To the Family of [Participant's Name] and sent to the participant's address.*

Writing the Letter

There are two condolence form letters used. One is for those who have passed away recently (less than 4 months) and the other is for those who passed away more than 4 months ago. These are Word documents titled "Condolence Letters May 2016" and "Condolence Letters—Later May 2016," for example *(See Appendix XX).*

Make sure to change only the following information in each letter:

- The date
- The name and address of the participant and the person who receives the letter
- The participant's name in the second sentence of the first paragraph
- The participant's last name in the first sentence of the second paragraph
- "His" or "her" in the second sentence of the second paragraph.

Printing the Letter

Once written, print out on plain paper a copy of the letter. Then photocopy this copy onto FHS letterhead. This letterhead copy is the one you will mail.

Make one copy of the letterhead copy for FHS Medical Records. At the top of each letter in the right-hand corner write the participant's PTS number. Highlight that number and their name in the body of the letter and give to Medical Records.

On the plain paper copy, write the participant's PTS number and highlight that and their name in the body of the letter. This is the Recruitment team's copy.

Mailing the Letter

Tri-fold the letter and place in an FHS envelope. Write Recruiter initials above the return address. Hand-write the name and address on the envelope but do not seal the envelope. Bring it to the second floor and place it in the outgoing mailbox by the stamp machine.

Recording the Letters

Once the letter has been sent, go to the Roster screen and write in all-caps on the Comment line: "CONDOLENCE LTR SNT month/year".

Go into the Excel document for that year. (For instance, all of 2016 names are listed in the document "2016 Condolence Letters Entered into PTS".) Enter in the date the letter was mailed, the PTS number, and the participant's name. Print just that month or copy and paste that month into a Word document and print that. Attach the list to the Recruitment team's copy of the letters along with the monthly and weekly reports, and file them.

9.0 Tracking

The participant's contact information is maintained in several ways:

1) Exam Recruitment: any study (core and ancillary) that is making recruitment calls to participants always verifies address and phone numbers during the recruitment call.
2) At the start of the Core Exam, the participant goes through the admitting process. The admitting form asks for participants to identify 2 contact persons (a contact person is defined as someone not living with the participant but who has a close enough relationship that they would know the participant's location if they were to move). In admitting, the participant will verify family members' addresses, some of whom are also in the study.
3) Health Updates: When filling out a health update with participants, their address, phone numbers, email, and a contact person are verified on this form.
4) Post Card mailing: The Recruitment office mails a postcard to all out-of-state participants in the spring of each year of the exam cycle. There is also an additional final post card mailed to any participant who has not scheduled for the current exam. The postage is specialized in that we request that the post office automatically return the mail if there is an address change, including the new address, if available. A recruiter may also mail a postcard to a participant if all phone numbers etc., are lost.
5) An FHS newsletter is mailed annually. The postage is specialized in that we request that the post office automatically return the mail if there is an address change, including the new address, if available.

10.0 Appendix (*TO BE REVISED*)

1 - 1234

Dear Mr. Xxxxxxx,

We thank you for participating in the Framingham Heart Study. Your exam appointment is scheduled for Monday, January 23, 2020 at 7:30 am.

The Framingham Heart Study's address is 73 Mt. Wayte Avenue, in the **Perini Building**. The Framingham Heart Study offices are **located in the wing at the Franklin Street side** of the building. **There is reserved parking for participants behind the Franklin Street wing.** Please see the enclosed map. The building is handicap accessible.

You should bring slippers and if you choose, bring your own robe. In order to perform certain tests, we ask that you **NOT** eat after 8:00 P.M. the previous evening. You may have **water**, **decaffeinated black coffee or tea (no creamer, milk or sugar) that evening and again in the morning** before your appointment. A urine sample will be collected when you arrive.

PLEASE TAKE ANY PRESCRIPTION MEDICATIONS AS YOU NORMALLY WOULD.

Using the enclosed **MEDICATION BAG,** please bring all prescription and nonprescription medications you currently take or have taken in the past month **in their original containers. They will be returned to you before you leave.**

ON THE BACK OF THIS SHEET, please list information regarding hospitalizations and major illnesses you have experienced in the past. **PLEASE BRING THIS LETTER WITH YOU TO YOUR APPOINTMENT.** If you need help completing this form, Clinic staff can assist you at the time of your appointment.

If you have any questions, please call [redacted]

Sincerely yours,

OVER →

Doctor(s)/Health Care Provider you want your report sent to:

Name	Address	Telephone

Hospitalizations, Emergency Room Visits, or Day Surgeries since 01/23/2012:

Date	Reason	Hospital Name & Address	Doctor's Name

Doctor's Office Visits:

Date	Reason	Doctor's Name

Framingham Heart Study
Offspring Exam 10, Omni 1 Exam 5
RESEARCH CONSENT FORM

Welcome Back to the Framingham Heart Study

Together we are helping to fight heart disease and other major diseases and health conditions through research.

Basic Information

Title of Project: Framingham Heart Study

IRB Number: H-32132

Sponsor: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)

Principal Investigator: Vasan S. Ramachandran, MD
fhs@bu.edu
73 Mount Wayte Avenue, Suite 2
Framingham, MA 01702

Study Phone Number:

PI Phone Number:

Why is the research study being done?

The Framingham Heart Study is a long-term research study. The purpose of the study is:

(1) To help understand how heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other major diseases and health conditions develop; and

(2) To examine DNA and its relationship to the risks of developing these diseases and other health conditions.

The research examination that will be conducted as part of this study is not clinical care. The tests are for research purposes only. We do not provide medical services. This research examination does not take the place of medical care by your own health care provider.

About your consent

Please read this research consent form carefully. It tells you important information about the research study. Taking part in a research study is voluntary. The decision whether or not to take part in all or any part of the research exam is entirely up to you. If you choose to take part, you

can decide to stop at any time. Your decision will be honored and respected. There will be no penalty to you if you decide to stop or not to take part.

If I have questions or concerns about this research study, whom can I call?

If you have any questions about the research or about this form, please ask us. You can call us with your questions or concerns. You can ask questions as often as you want.

You can call a study staff member directly at

The Framingham Heart Study is led by investigators from Boston University and the National, Heart, Lung, and Blood Institute at the National Institutes of Health. Dr. Vasan S Ramachandran and Dr. Daniel Levy are in charge of the research study. [redacted]

[redacted] You will be talking to someone at the Boston Medical Center and Boston University Medical Campus IRB. The IRB is a group that helps monitor research. You should call or email the IRB if you want to find out about your rights as a research subject. You should also call or email if you want to talk to someone who is not part of the study about your questions, concerns, or problems.

What will happen in this research study?

You will need to fast for 10 hours before you come to the study appointment for the blood draw. You can continue to drink water while fasting and take your usual medication on the morning of your visit.

Your research examination will take place at the FHS Research Center at 73 Mount Wayte Avenue, Framingham, MA, by phone or video conference (also referred to as a televisit), or in your home or other residence. The full onsite research exam will take around 4-5 hours to complete or the exam may also be split into multiple pieces: a 2-hour televisit and 2.5 hour in-person visit at the Research Center. Exam components that may be completed remotely will be included during the televisit and components that require in-person assessment will be conducted at the Research Center or offsite home or other residence.

As before, we will

- draw a sample of blood for genetic and laboratory tests to better understand risk factors for heart disease and other diseases under investigation (for example, the amount and function of different types of cholesterol in your blood). The total blood draw will be up to 80mL, which is about 5.4 tablespoons. The blood draw will occur soon after your arrival.
- collect a urine sample
- measure your height, weight, and waist
- measure grip strength
- complete an electrocardiogram (ECG)
- record your blood pressure
- update your medical history information

- complete a test of cardiac vascular function (tonometry) that examines heart function using ultrasound scanning (echocardiogram) and tests blood vessel (artery) stiffness by recording the blood pressure and flow waveforms
- ask you to sign a form to allow FHS to obtain copies of medical records, including Medicare records. The release form is valid to obtain these records unless canceled by you.
- contact you later by mail, email, or by phone (call or text) to obtain additional information or to invite you to participate in further FHS related studies. You may also be invited to return for another examination in the future.

Surveys
We will also be asking you to complete questionnaires such as physical function, diet, exercise, memory and mood, and your lifestyle habits, including whether you smoke or use alcohol. Some of the questionnaires you will have seen before and others will be new to you.

Some of your responses will be recorded using a digital audio recorder. Recordings will be analyzed in conjunction with other study information. We will also use recordings to make sure that your responses are accurately documented.

There are some new research activities.

1. Fibroscan: We are interested in improving our understanding of the factors that can help predict the development of liver fat and liver fibrosis (scarring) for this study, you will have a test called a Fibroscan. The Fibroscan measures the presence of fat or scarring in the liver. A painless pulse is generated on your skin that travels to the liver and measures how stiff your liver is.

   What risks can I expect? There may be minor discomfort from the application of lubricating jelly and pressure on the skin from the Fibroscan probe. However, there are no known risks associated with the Fibroscan.

   There are some conditions that may interfere with the ability of the device to obtain valid measures. They include being pregnant, having fluid in the abdominal cavity (ascites), and having implanted medical devices, such as a heart pacemaker. We will ask you to confirm if you have any of these conditions and if you do, we will not complete the Fibroscan.

2. Pain Assessment Study: We are interested in learning about pain people may be experiencing in their daily lives, and to better understand why some people have pain, more pain, or pain in more parts of their body, than other people do. We will ask some questions about pain and assess your sensitivity to pressure on your skin. To test your sensitivity to pressure, a small device will be pressed against a muscle on your shoulder to measure how much pressure is applied before you feel any discomfort.

   What risks can I expect? Although rare, there is the potential for skin irritation and redness or bruising during testing. Bruising or discomfort could potentially result from application of the pressure meter during pressure pain threshold testing and/or blood pressure cuff inflation.

3. Brain Health Study: We are interested in finding a way to define brain health beyond the evaluation of cognitive testing. We will ask you to participate in a number of sensory

motor tests that capture your brain health, including testing your vision, hearing, and motor function. You will have eye testing (without dilatation); hearing testing (using an iPad and headphones); and physical function testing (includes gait speed assessment on an electronic gait mat, during normal walk and while doing a mental task like counting and timed chair stands).

What risk can I expect? There are no risks involved in eye and hearing testing. Gait testing has a minimal risk of falling. All precautions will be taken to prevent falls. A study staff member will stand near you to prevent you from falling and help you if needed.

4. Electronic FHS (eFHS) Study: If you live in the US, have an email account with access to a daily Internet connection or have a smartphone, we will invite you to take part in the eFHS study. Taking part requires that you visit a web platform, download apps and use wireless devices. The apps will require you to complete surveys regarding lifestyle and health, and the devices will measure heart rate, blood pressure, weight, and physical activity.

   What risks can I expect? There are no known risks to taking part in this study.

5. Bone Scan: We are interested in learning about how the skeleton changes with aging. We will ask you to participate in two bone scans to examine the bone structure in your lower leg and lower arm. The scan is a non-invasive and painless test, and provides a detailed image of the "micro-architecture" inside the bone. Each scan takes about two minutes and requires that you keep as still as possible.

   What risks can I expect? Bone scans involve the use of x-rays, a form of energy also called radiation. The radiation dose for the two scans together will be less than 10 μSv, which is equivalent to 2-3 days of background radiation that individuals experience in the U.S. Since the amount of radiation from the bone scans is so small, there are no known long-term effects of this radiation on your health.

Some of the study components described in this section "What will happen in this research study?" may not be administered during televisits, due to the need to take certain measurements in person. Also, some of the study components may not be administered during offsite examinations taking place at your home or care facility, due to large equipment that cannot be transported outside of the research center. For example, Fibroscan, Tonometry, and Computed Tomography.

Overall Examination Risks and Discomforts
General Risks: The research exam is time consuming and repetitive. Other discomforts include headaches, feeling hungry due to fasting, fatigue and chill during the visit.

CT bone scans involve exposure to radiation. Since the amount of radiation is so small, equivalent to 2-3 days of background radiation there are no known long-term effects of this radiation on your health. However due to potential risk to a fetus, pregnant women, as determined by self-report or by a positive pregnancy test, will be excluded from this test.

We do not expect any risk of injury as a result of your participation in the study. However, first aid will be available.
Unknown Risks: There may also be some risks that we are unable to determine at this time.

Genetic Studies

You may have already provided consent for the collection of biological samples for DNA research or the creation of Induced Pluripotent Stem Cells (iPS cells). We plan to continue to do genetic research on the DNA from your biological samples. The biological samples include blood cells, tissue cells, etc. DNA is the material that makes up your genes. Genes are passed from parent to child. All living things are made of cells. Genes are the part of cells that contain the instructions which tell our bodies how to grow and work and determine physical characteristics such as hair and eye color.

Also, if you agree, we will process white blood cells from a sample of your blood to become stem cells in the laboratory. The resulting cells are known as Induced Pluripotent Stem Cells (iPS cells), and they will be used in the laboratory to act like cells from other organs, such as liver cells, fat cells, heart cells, lung cells, vascular cells, gut cells, nerve cells, different types of blood cells, and many other engineered or naturally occurring cell types. These cells and the cell products that can be obtained from them such as RNA, proteins, and metabolites may be studied in laboratories to learn more about the causes of health and diseases of these organs.

Your cells will be stored indefinitely in a stem cell repository at Boston University. Your cells may also be stored in a central repository or bank.

If you agree, your stored tissues, cells and any resulting iPS cell lines or their derivatives could be used in future related and unrelated research studies including:

- Injecting or transplanting the stem cells or their derivatives into animals for research purposes. Your samples may be used in research that involves genetic manipulation but they will not be used to clone or to otherwise create an entire human being.
- Testing for genetic and DNA composition. Genes may be analyzed and/or manipulated to study normal function or development, and some of the DNA in the stem cells or their derivatives may be altered.
- Other uses involving research or development of commercial products for the diagnosis, prevention, or treatment of various diseases.
- Samples (blood cells, the iPS cells, or their derivatives) obtained from you in this study may be used in the development of one or more diagnostic or therapeutic products which could be patented and licensed by those involved in the research or development of such products. There are no plans to provide financial compensation to you should this occur.

How will I learn the results of this study?

The main way results of research from this study are reported is in scientific publications and presentations at scientific meetings. Summary findings are also sometimes described in our newsletters and on our study website.

We will also report some routine research test measurements to you and/or your health care provider at the time of the exam or after your visit. These may include, for example, blood pressure and cholesterol.

In some cases, if we determine it to be appropriate, we may report to you and/or your health care provider research findings as they relate to you, if you give your permission. This information, if it is reported, might be reported long after your visit for a number of reasons. As an example, it might take years of work to analyze information and arrive at research findings, possibly using newly developed scientific methods.
Our genetic research might generate findings that could be relevant to you and possibly your family members, such as information about a particular genetic variant that might put you at risk of a serious health condition. At this time, we believe that most of the genetic research findings do not have medical importance to individuals, but the field of genetics is changing rapidly.

We currently do not have specific plans to contact you or your health care provider about genetic or non-genetic research findings other than some routine research test measurements. In general, we cannot commit to providing any other research findings to you. In determining whether we share additional research information with you, we will take into account a number of considerations on a case-by-case basis. These might include whether the findings were based on tests that are clinically acceptable, accurate and reliable, whether the findings reveal a significant risk of a serious health condition, whether there is, at the relevant time, a recognized treatment or prevention intervention or other available actions that have the potential to change the clinical course of the health condition, whether reporting or not reporting the results is likely to increase the risk of harm to you, and other relevant factors that we might not be able to predict at this time. In the cases when genetic research findings are reported to you, a study investigator and genetic counselor will contact you to confirm your continued interest in hearing about genetic research results. If you confirm your interest, the study staff will inform you of the research results and recommend next steps such as obtaining confirmatory clinical testing and speaking with your personal healthcare provider.

Research test measurements and findings are not the same as clinical test results. As such, our research examination is not necessarily performed by individuals with clinical training and qualifications, and many parts of the examination do not meet the standards for certified clinical testing. For these reasons, our research tests should not be relied on to make any diagnosis, treatment, or health planning decisions. We do not provide health care or give medical advice or genetic testing or provide counseling. If you or your health care provider decides that follow-up tests or treatments are necessary, then you (or a third party such as a health insurance carrier or Medicare) will be responsible for the cost.

How are my samples and information shared with other researchers?

Samples and information will be kept indefinitely. If you agree, your data and donated blood, blood cells, resulting iPS cells or their derivatives, urine, and any other specimens may be shared with other researchers. These include other academic, non-profit, and for-profit entities, including but not limited to hospitals, universities, cell/tissue storage banks and repositories, databanks and data repositories and businesses, whether for related or unrelated research studies. The cell/tissue storage banks and repositories, databanks and data repositories, include but are not limited to, NIH repositories dbGaP and BioLINCC. Internal and external researchers may request data and materials for research. The repositories have standard operating procedures to protect your confidentiality. Your data and samples will not be labeled with your name or other direct personal identifiers, only a code.

Coded audio recording information will be analyzed by qualifying collaborators inside and outside of BUMC. Your name and other direct personal identifiers will not be shared with these entities.

You have the right to refuse to allow your data and samples to be used or shared for further research. Please check the appropriate box in the selection below.

If you give your permission to allow your data and biological samples to be used or shared for further research, you may withdraw your permission at any time by contacting the FHS investigators. However, if your data or samples have already been released to other researchers, we will not be able to instruct the other researchers to stop using them, to destroy them or products made from them. Your data and samples will not include your name or other direct identifiers.

What risks can I expect?

General risks and individual risks related to new activities are discussed above.

Participating in genetic research could have a negative impact on you, your family, and your loved ones. The genetic studies might result in research findings that relate to your risk of a serious health condition or other genetic information that we might consider to be appropriate to report to you and your health care provider, if you wish us to report them (see below). This could present you with some difficult decisions regarding the available information and the disease risks you and your family members might face. Knowledge of genetic research findings can provoke anxiety and influence decisions regarding marriage, family planning, and other matters. There is a potential risk that your genetic information could be used to your disadvantage. For example, if genetic research findings suggest a serious health problem, that could be used to make it harder for you to get or keep a job or insurance. Both Massachusetts state laws and federal laws, particularly the Genetic Information Nondiscrimination Act (GINA), generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. These laws will generally protect you in the following ways:

1. Health insurance companies and group health plans may not request your genetic information that we get from this research.
2. Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
3. Massachusetts employers with 6 or more employees (or 15 or more employees in other states, under GINA) may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that neither Massachusetts law nor GINA protects you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Thus, life insurance, disability insurance, and long-term care insurance companies may legally ask whether you have had genetic testing and deny coverage for refusal to answer this question.

How is my information protected?

We will store your information in ways we think are secure. We label your samples and information with a code, and we keep the key to the code in a password protected database.

Only approved staff is given the password. We use other safeguards at our facilities and for our information technology and systems to protect the privacy and security of your information.

We do not sell, rent, or lease your contact information.

If information from this study is published or presented at scientific meetings, and when your samples and information are shared with other researchers and deposited in data and specimen banks and repositories, your name and other direct personal identifiers will not be used.

However, we cannot guarantee total privacy. We may provide access to your information in order to do the study and to make sure we do the study according to certain standards set by ethics, law, and quality groups. Information may be made available to researchers that are part of this study, the Institutional Review Board that oversees this research, research and non-research staff and organizations who need the information to do their jobs for the conduct and oversight of the study, people or groups that we hire to do work for us (such as data or biosample storage companies, insurers, and lawyers), and Federal and state agencies as required by law or if they are involved in the research or its oversight. In most cases, any information that is given out to others is identified by code and not with your name or other direct personal identifiers. Once information is given to outside parties, we cannot promise that it will be kept private. Please be aware that your personal information may be given out if required by law (e.g., to prevent possible injury to yourself or others).

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. All studies funded by the National Institutes of Health that involve identifiable information or biological samples are covered by a CoC. The CoC provides how we can share research information or biological samples. Because we have a CoC, we cannot give out research information or biological samples that may identify you to anyone that is not involved in the research except as we describe below. Even if someone tries to get your information or biological samples in connection with a legal proceeding, we cannot give it to them. The CoC does not prevent you from sharing your own research information.

If you agree to be in the study and sign this form, we will share information and biological samples that may show your identity with the following groups of people:

- People who do the research or help oversee the research, including safety monitoring.
- People from Federal and state agencies who audit or review the research, as required by law. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health.
- Investigators who will get your data and your biological samples as we described in the section "*What will happen in this research study?"* These people are expected to protect your information and biological samples in the same way we protect it.
- Any people who you give us separate permission to share your information.

You should know that we are required to report information about child abuse or neglect; elder abuse; specific reportable diseases; or harm to others.

We will share research data where we have removed anything that we think would show your identity. There still may be a small chance that someone could figure out that the information is about you. Such sharing includes:

- Publishing results in a medical book or journal.

- Adding results to a Federal government database
- Using research data in future studies, done by us or by other scientists.
- Using biological samples in future studies, done by us or by other scientists.

Samples that are collected from you in this study will be analyzed to find out information about your genetic makeup. Your genetics and health information, without your name or other data that could easily identify you, will be put in a database run by the National Institutes of Health (NIH). This may include your whole genome information. Other researchers can ask the NIH to get your information from the database. You should know that it is possible that your genetics information might be used to identify you or your family, though we believe it is not too likely that this will happen. Once your information is given to the NIH database, you can ask to have NIH stop sharing it, but NIH cannot take back information that was already shared.

Patenting Discoveries

Research from this study may, one day, result in new tests to diagnose or predict diseases. It may also lead to the development of new ways to prevent or treat diseases. As is true of all federally-funded research, researchers and their employers are permitted by Federal law to patent discoveries from which they may gain financially. You and your heirs will not benefit financially.

What are the possible benefits from being in this research study?

While you will not receive any direct benefit as a result of your participation in this study; we hope that this study will help us better understand what causes heart disease and other diseases and conditions and how to better prevent and treat them.

What are the costs of taking part in the study?

Costs that you may incur on the day of your participation include, but are not limited to, loss of work and transportation costs (gas, tolls, etc.).

You will not be paid for your participation in this study.

No special arrangement will be made by the Framingham Heart Study for compensation or payment solely because of your participation in this study. If you think you have been injured by being in this study, please let the investigators know right away. Boston University and the sponsors do not offer a program to provide compensation for the cost of care for research related injury or other expenses such as lost wages, disability, pain, or discomfort. You will be sent a bill for the medical care you receive for research injury if your medical insurance does not pay for your medical care. This does not waive any of your legal rights.

How long will I be in the study?

FHS is a long-term study.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

The investigator may decide to discontinue your participation without your permission because he/she may decide that staying in the study will be bad for you, or the sponsor may stop the study.

Please read the following statements and check the appropriate box below:

1) I agree to participate in the FHS examination, including the collection of data, blood, urine samples, and various research tests and measurements. I agree to the use of all data, samples, and research materials for studies of the factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other diseases and health conditions.

   | _| YES | _| NO (*For Internal Use - Office Code 0*)

2) I agree to allow my data, blood, DNA and other genetic material, iPS cells and their derivatives, urine samples, and any other specimens to be used in genetic research, of factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other diseases and health conditions.

   | _| YES | _| NO (*For Internal Use - Office Code* 3)

3) I agree to allow researchers from commercial companies to have access to my data, blood, DNA and other genetic material, iPS cells and their derivatives, urine samples, and any other specimens for research. I understand that my data and specimens will be shared without my name or direct personal identifiers.

   | _| YES | _| NO (*For Internal Use - Office Code 4*)

4) I agree to allow the FHS to release the findings of non-genetic research tests and examinations to me and/or my physician, clinic, hospital, or other health care provider.

   | _| YES | _| NO (*For Internal Use - Office Code 30*)

5) I agree to allow the FHS to provide me, and with my permission, my physician, clinic, hospital, or other health care provider information relating to genetic research findings as they may relate to me.

   | _| YES | _| NO (*For Internal Use - Office Code 31*)

Subject: _____
Printed name of subject

By signing this consent form, you are indicating that

- you have read this form (or it has been read to you)
- your questions have been answered to your satisfaction
- you voluntarily agree to participate in this research study
- you permit the use and sharing of information that may identify you as described, including your health information.

To be completed by subject if personally signing

_____ _____
Signature of subject Date

To be completed by LAR if subject does not personally sign
I am providing consent on behalf of the subject.

_____ _____
Printed name of Legally Authorized Representative (LAR) Relationship to Subject

_____ _____
Signature of Legally Authorized Representative Date

Researcher: _____
Printed name of person conducting consent discussion

To be completed by researcher if subject personally signs
I have personally explained the research to the above-named subject and answered all questions. I believe that the subject understands what is involved in the study and freely agrees to participate.

_____ _____
Signature of person conducting consent discussion Date

To be completed by researcher if subject does not personally sign
I have personally explained the research to the above-named subject's Legally Authorized Representative and answered all questions. I believe that the Legally Authorized Representative understands what is involved in the study and freely agrees to have the subject participate.

I consider that the above-named subject (check one):
☐ is capable of understanding what is involved in the study and freely agrees to participate.
☐ is not capable of understanding what is involved in the study.

_____ _____
Signature of person conducting consent discussion Date

Framingham Heart Study
Offspring Exam 10, Omni 1 Exam 5
Brain Health Study

RESEARCH CONSENT FORM ADDENDUM

Basic Information

Title of Project: Multidimensional Assessment of Brain Health as a Marker of Dementia Risk and Resilience

IRB Number: H-40757

Sponsor: National Institute on Aging (NIA), National Institutes of Health (NIH)

Principal Investigator: Sudha Seshadri, M

Please take time to review this information carefully. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Voluntary Participation - You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are entitled.

The PI of the Brian Health Study is Dr. Sudha Seshadri who is Professor of Neurology at the University of Texas Health Sciences Center, San Antonio, TX and also an adjunct Professor of Neurology at Boston University School of Medicine. The Program Manager supervising this effort at the Framingham Heart Study site is xxxx and the PI of the Framingham site for this study is Dr. Vasan Ramachandran, MD who is also the PI of the overall Framingham Heart Study.

Study Phone Number:

Overview of the Brain Health Study

We are interested in finding a way to define brain health beyond the evaluation of cognitive testing. We will ask you to participate in a number of sensory motor tests that capture your brain health, including testing your vision, hearing, and motor function. You will have eye testing (without dilatation); hearing testing (using an iPad and headphones); and motor function testing (includes gait speed assessment on an electronic gait mat, during normal walk and while doing a mental task like counting.) As described in the main consent form, we may also report some routine research test measurements to you and/or your health care provider at the time of the exam or after your exam

The Brain Health Study within the Framingham Heart Study Offspring Exam 10, Omni 1 Exam 5 is conducted in collaboration with The University of Texas Health Science Center at San Antonio.

All procedures described below will be performed for research purposes only.
A. Vision Testing:

Optical Coherence Tomography Angiography (OCTA):
This exam will be performed without dilating eye drops. You will be asked to rest your chin and forehead on a support that is attached to the OCT machine. You will be asked to fixate your eyes on a target for a few moments and as a camera scans and takes images of the retina, the back of your eye. It also measures blood flow in the eye and is a completely non-invasive measurement that is approved by the U.S. Food and Drug Administration (FDA) as a rapid method of assessing retinal capillary density

B. **Motor Testing**

In ***Gait Testing***, you will be asked to walk on a gait mat (that appears like a regular rug or mat) that has pressure sensors below it. A computer and software connected to the mat will capture the different aspects of the walk including speed, step length, step width, etc. You will be asked to walk at your usual pace, fast pace and while doing cognitive tasks like counting backwards.

C. Hearing Testing
Using a portable tablet-based system and earphones we will present a **pure tone** to the **ear** measuring the lowest intensity in decibels (dB) at which this **tone** is perceived 50% of the time. This measurement is called **threshold**.

Risks of Participation in this research

Informational risks related to the study
Your data will be assigned a code number. Your name, medical record number, or other information that easily identifies you will not be stored with your samples or data. The key that links your identifying information to the code number will be stored securely in a separate file and will not be shared with researchers that are not part of our study team.
The main risk of allowing us to use your data for research is a potential loss of privacy. This risk is serious but rare because we take many steps to protect your information. We protect your privacy by coding your data and removing personal identifiers. Research results obtained in this study will not be placed in your medical record unless we contact you with a finding of high medical importance. We do not think that there will be further risks to your privacy by sharing your data with other researchers; however, we cannot predict how this data will be used in the future.

Risks of Study Procedures
There is also minimal risk of falling during the gait testing, but we will take the same precautions described above to prevent falls by walking behind and to the side and assisting if required.

For more information about risks and side effects, ask one of the researchers or study staff. We will tell you about any significant new findings which develop during the course of this research which may relate to your willingness to continue taking part.

What if a research-related injury occurs?
The researchers have taken steps to minimize the known or expected risks and we expect no injuries from these studies. However, you may still experience problems or side effects, even though the researchers are careful to avoid them. in the event of a research-related injury or if you experience an adverse reaction, please immediately contact study staff. See the section "Contact Information" for phone numbers and additional information. You may also need to tell your regular doctors.

If you are injured or made sick from taking part in this research study, medical care will be provided. This care may be billed to you or your insurance. Depending on the circumstances, this care may be provided at no cost to you. We do not offer a program to provide compensation for the cost of care for research related injury. The study staff can provide you with more information.

If you sign this form, you do not give up your right to seek additional compensation if you are harmed as a result of being in this study

Information about how this study will use your Protected Health Information (PHI)
Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of monitoring research may want to see study records which identify you as a subject in this study.

Research policies require that private information about you be protected and this is especially true for your health information. However, the law sometimes allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study.

What is Protected Health Information (PHI)?
Protected Health Information is information about a person's health that includes information that would make it possible to figure out who the person is. According to the law, you have the right to decide who can see your protected health information. If you choose to take part in this research study, you will be giving your permission to the investigators and the research study staff (individuals carrying out the study) to see and use your health information for the study. In carrying out this research, the health information we will see and use about you will include:

- your medical history and blood work,
- results of eye, ear and gait assessment tests,
- information from interviews or from questionnaires,
- demographic information like your age, sex

We will get this information from the data collected today and over the years at the Framingham Heart Study

How will your PHI be protected?
In an effort to protect your privacy, the study staff will use code numbers instead of your name, to identify your health information. Initials and numbers will be used on any photocopies of your

study records, and other study materials containing health information that are sent outside the institutions listed above for review or testing. If the results of this study are reported in medical journals or at meetings, you will not be identified.

Parts of your PHI may be photocopied and sent to a central location or it may be transmitted electronically, such as by e-mail, fax, or other secure means of transmission. The groups receiving your health information may not be obligated to keep it private. They may pass information on to other groups or individuals not named here.

How will your PHI be shared with other Researchers?
Because it is research, we will be unable keep your PHI completely confidential. We may share your health information with people and groups involved in conducting and overseeing this research study including:

- the following collaborators at other institutions that are involved with the study: The University of Texas Health Science Center at San Antonio, Boston University School of Medicine, Massachusetts Eye and Ear Infirmary and University of Southern California
- the members of the local research team;
- the Institutional Review Board and the Compliance Office of the University of Texas Health Science Center at San Antonio, and other groups that oversee how research studies are carried out; and
- the Research offices at the University of Texas Health Science Center at San Antonio

If you decide to participate in this study, you will be giving your permission for the groups named above, to collect, use and share your health information for research purposes. If you choose not to let these groups collect, use and share your health information as explained above, you will not be able to participate in this research study.

Do you have to allow the use of your health information?
You do not have to allow (authorize) the researchers and other groups to see and share your health information. If you choose not to let the researchers and other groups use your health information, there will be no penalties, but you will not be allowed to participate in the Brain Health Study portion part of the Framingham Heart Study Examination.

After you enroll in this study, you may ask the researchers to stop using your health information at any time. However, you must provide this in writing and send your letter to ***Vasan Ramachandran, Principal Investigator, Framingham Heart Study, 73 Mt Wayte Ave, Suite 2, Framingham, MA 01702.*** If you tell the researchers to stop using your health information, your participation in this part of the Framingham Heart study will end and the study staff will stop collecting new health information from you and about you for this study. However, the study staff will continue to use the health information collected up to the time they receive your letter asking them to stop.

Can you ask to see the PHI that is collected about you for this study?
The federal rules say that you can see the health information that we collect about you and use in this study. Contact the study staff if you have a need to review your PHI collected for this study. If you ask for research information that is not in your medical record, we might not

provide it to you, but we will explain why not. You may use the contact information on the first page of this form to find out how to get your health information.

How long will your PHI be used?
By signing this form, you agree to let us use and disclose your health information for purposes of the study until the end of this study; at this time we do not have any specific end date and will continue using your data until it is no longer of scientific value.

Contact Information
If you have questions now, feel free to ask us. If you have additional questions later or you wish to report a problem or complaint which may be related to this study please contact:

FHS Neurology Study Manager, Timothy Kowalczyk at 508-935-3410.

The University of Texas Health Science Center committee that reviews research on human subjects (Institutional Review Board) will answer any questions about your rights as a research subject, and take any concerns, comments or complaints you may wish to offer. You can contact the IRB by calling xxxxxxxxx.

Research Consent & Authorization Signature Section

If you agree to participate in this research and agree to the use of your protected health information in this research sign this section. You will be given a signed copy of this form to keep. You do not waive any of your legal rights by signing this form.

SIGN THIS FORM ONLY IF THE STATEMENTS LISTED BELOW ARE TRUE

- You have read the above information.
- Your questions have been answered to your satisfaction.

Adult Signature Section

- You have voluntarily decided to take part in this research study.
- You authorize the collection, use and sharing of your protected health information as described in this form.

Printed Name of Subject	Signature of Subject	Date

Surrogate Signature Section

- You are voluntarily giving your consent for another person to participate in this study because you believe this person would want to take part if able to make the decision and you believe it is in this person's best interest.
- You are authorizing the collection, use and sharing of another person's protected health information as described in this form.

Printed Name of Subject	Signature of **Subject**, indicating Assent *(If incapable of signing, person obtaining consent should initial here)*	Date
Printed Name of Legally Authorized Representative (LAR)	Signature of Legally Authorized Representative (LAR)	Date

Researcher

Printed Name of Person Obtaining Consent and Authorization	Signature of Person Obtaining Consent & Authorization	Date

BMC and BU Medical Campus IRB
IRB NUMBER: H-32132
IRB APPROVAL DATE: 07/21/2021

Framingham Heart Study
Offspring Exam 10, Omni 1 Exam 5
Bone Study Informed Consent Form ADDENDUM

Basic Information

Title of Project: Framingham Heart Study

IRB Number: H-32132

Sponsor: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)

Principal Investigator: Vasan S. Ramachandran, MD

[redacted]

Study Phone Number: xxx xxx xxxx

PI Phone Number: xxx xxx xxxx

Overview of the Bone Study at the Framingham Heart Examination

We are interested in learning about how the skeleton changes with aging. We will ask you to participate in two bone scans to examine the bone structure in your lower leg and lower arm. The scan is a non-invasive and painless test, and provides a detailed image of the "micro-architecture" inside the bone. Each scan takes about two minutes and requires that you keep as still as possible.

The research examination that will be conducted as part of this study is not clinical care. The tests are for research purposes only. We do not provide medical services. This research examination does not take the place of medical care by your own health care provider.

About your consent

Please read this research consent form carefully. It tells you important information about the research study. Taking part in a research study is voluntary. The decision whether or not to take part in all or any part of the research exam is entirely up to you. If you choose to take part, you can decide to stop at any time. Your decision will be honored and respected. There will be no penalty to you if you decide to stop or not to take part.

If I have questions or concerns about this research study, whom can I call?

If you have any questions about the research or about this form, please ask us. You can call us with your questions or concerns. You can ask questions as often as you want.

You can call a study staff member directly at xxx xxx xxxx, or you can send an email to FHS@bu.edu.

The Framingham Heart Study is led by investigators from Boston University and the National, Heart, Lung, and Blood Institute at the National Institutes of Health. Dr. Vasan S Ramachandran and Dr. Daniel Levy are in charge of the research study. You can contact Dr. Ramachandran at [redacted]

You may also call [redacted] You will be talking to someone at the Boston Medical Center and Boston University Medical Campus IRB. The IRB is a group that helps monitor research. You should call or email the IRB if you want to find out about your rights as a research subject. You should also call or email if you want to talk to someone who is not part of the study about your questions, concerns, or problems.

Overall Examination Risks and Discomforts
Bone scans involve the use of x-rays, a form of energy also called radiation. The radiation dose for the two scans together will be less than 10 μSv, which is equivalent to 2-3 days of background radiation that individuals experience in the U.S. Since the amount of radiation from the bone scans is so small, there are no known long-term effects of this radiation on your health. However due to potential risk to a fetus, pregnant women, as determined by self-report or by a positive pregnancy test, will be excluded from this test.

We do not expect any risk of injury as a result of your participation in the study. However, first aid will be available.

Unknown Risks: There may also be some risks that we are unable to determine at this time.

How is my information protected?

We will store your information in ways we think are secure. We label your samples and information with a code, and we keep the key to the code in a password protected database. Only approved staff is given the password. We use other safeguards at our facilities and for our information technology and systems to protect the privacy and security of your information.

We do not sell, rent, or lease your contact information.

If information from this study is published or presented at scientific meetings, and when your samples and information are shared with other researchers and deposited in data and specimen banks and repositories, your name and other direct personal identifiers will not be used.

However, we cannot guarantee total privacy. We may provide access to your information in order to do the study and to make sure we do the study according to certain standards set by ethics, law, and quality groups. Information may be made available to researchers that are part of this study, the Institutional Review Board that oversees this research, research and non-research staff and organizations who need the information to do their jobs for the conduct and oversight of the study, people or groups that we hire to do work for us (such as data or biosample storage companies, insurers, and lawyers), and Federal and state agencies as required by law or if they are involved in the research or its oversight. In most cases, any information that is given out to others is identified by code and not with your name or other direct personal identifiers. Once information is given to outside parties, we cannot promise that it

will be kept private. Please be aware that your personal information may be given out if required by law (e.g., to prevent possible injury to yourself or others).

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. All studies funded by the National Institutes of Health that involve identifiable information or biological samples are covered by a CoC. The CoC provides how we can share research information or biological samples. Because we have a CoC, we cannot give out research information or biological samples that may identify you to anyone that is not involved in the research except as we describe below. Even if someone tries to get your information or biological samples in connection with a legal proceeding, we cannot give it to them. The CoC does not prevent you from sharing your own research information.

If you agree to be in the study and sign this form, we will share information and biological samples that may show your identity with the following groups of people:

- People who do the research or help oversee the research, including safety monitoring.
- People from Federal and state agencies who audit or review the research, as required by law. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health.
- Investigators who will get your data and your biological samples as we described in the section "*What will happen in this research study?"* These people are expected to protect your information and biological samples in the same way we protect it.
- Any people who you give us separate permission to share your information.

You should know that we are required to report information about child abuse or neglect; elder abuse; specific reportable diseases; or harm to others.

We will share research data where we have removed anything that we think would show your identity. There still may be a small chance that someone could figure out that the information is about you. Such sharing includes:

- Publishing results in a medical book or journal.
- Adding results to a Federal government database
- Using research data in future studies, done by us or by other scientists.
- Using biological samples in future studies, done by us or by other scientists.

Samples that are collected from you in this study will be analyzed to find out information about your genetic makeup. Your genetics and health information, without your name or other data that could easily identify you, will be put in a database run by the National Institutes of Health (NIH). This may include your whole genome information. Other researchers can ask the NIH to get your information from the database. You should know that it is possible that your genetics information might be used to identify you or your family, though we believe it is not too likely that this will happen. Once your information is given to the NIH database, you can ask to have NIH stop sharing it, but NIH cannot take back information that was already shared.

Patenting Discoveries

Research from this study may, one day, result in new tests to diagnose or predict diseases. It may also lead to the development of new ways to prevent or treat diseases. As is true of all federally-funded research, researchers and their employers are permitted by Federal law to

patent discoveries from which they may gain financially. You and your heirs will not benefit financially.

What are the possible benefits from being in this research study?

While you will not receive any direct benefit as a result of your participation in this study; we hope that this study will help us better understand what causes heart disease and other diseases and conditions and how to better prevent and treat them.

What are the costs of taking part in the study?

Costs that you may incur on the day of your participation include, but are not limited to, loss of work and transportation costs (gas, tolls, etc.).

You will not be paid for your participation in this study.

No special arrangement will be made by the Framingham Heart Study for compensation or payment solely because of your participation in this study. If you think you have been injured by being in this study, please let the investigators know right away. Boston University and the sponsors do not offer a program to provide compensation for the cost of care for research related injury or other expenses such as lost wages, disability, pain, or discomfort. You will be sent a bill for the medical care you receive for research injury if your medical insurance does not pay for your medical care. This does not waive any of your legal rights.

How long will I be in the study?

FHS is a long-term study.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

The investigator may decide to discontinue your participation without your permission because he/she may decide that staying in the study will be bad for you, or the sponsor may stop the study.

Subject: _____
Printed name of subject

By signing this consent form, you are indicating that

- you have read this form (or it has been read to you)
- your questions have been answered to your satisfaction
- you voluntarily agree to participate in this research study
- you permit the use and sharing of information that may identify you as described, including your health information.

To be completed by subject if personally signing

_____ _____
Signature of subject Date

To be completed by LAR if subject does not personally sign
I am providing consent on behalf of the subject.

_____ _____
Printed name of Legally Authorized Representative (LAR) Relationship to Subject

_____ _____
Signature of Legally Authorized Representative Date

Researcher: _____
Printed name of person conducting consent discussion

To be completed by researcher if subject personally signs
I have personally explained the research to the above-named subject and answered all questions. I believe that the subject understands what is involved in the study and freely agrees to participate.

_____ _____
Signature of person conducting consent discussion Date

To be completed by researcher if subject does not personally sign
I have personally explained the research to the above-named subject's Legally Authorized Representative and answered all questions. I believe that the Legally Authorized Representative understands what is involved in the study and freely agrees to have the subject participate.

I consider that the above-named subject (check one):
☐ is capable of understanding what is involved in the study and freely agrees to participate.
☐ is not capable of understanding what is involved in the study.

_____ _____
Signature of person conducting consent discussion Date

Estudio del Corazon de Framingham,
examen 10 de Offspring, examen 5 de Omni 1

FORMULARIO DE CONSENTIMIENTO PARA LA INVESTIGACIÓN

Bienvenido nuevamente al Estudio del Corazón de Framingham

Juntos estamos ayudando a combatir las enfermedades cardíacas y otras enfermedades y problemas de salud importantes mediante la investigación.

Información básica

Título del proyecto: Estudio del Corazón de Framingham

Número de la IRB: H-32132

Patrocinador: Instituto Nacional del Corazón, los Pulmones y la Sangre (National Heart, Lung, and Blood Institute, NHLBI), Institutos Nacionales de Salud (National Institutes of Health, NIH)

Investigador principal: Vasan S. Ramachandran, MD [redacted]

Número de teléfono del estudio: [redacted]

Número de teléfono del IP: [redacted]

¿Por qué se está haciendo este estudio de investigación?

El Estudio del Corazón de Framingham es un estudio de investigación a largo plazo. Su propósito es el siguiente:

(1) ayudar a comprender cómo se desarrollan las enfermedades del corazón y los vasos sanguíneos, las enfermedades de los pulmones y la sangre, los accidentes cerebrovasculares, la pérdida de memoria, el cáncer y otras enfermedades y afecciones de salud importantes;

y

(2) examinar el ADN y su relación con los riesgos de desarrollar estas enfermedades y otras afecciones de salud.

El examen que se llevará a cabo como parte de este estudio de investigación no es igual a la atención médica en una clínica. Las pruebas son solo con fines de investigación. No ofrecemos servicios médicos. Este examen no reemplaza su control con su proveedor de atención médica.

Acerca de su consentimiento

Lea atentamente este formulario de consentimiento de investigación. Le brinda información importante sobre el estudio. La participación en un estudio de investigación es voluntaria. La decisión de participar o no, ya sea en parte o en la totalidad del examen, depende completamente de usted. Si usted elige participar, puede decidir dejar de hacerlo en cualquier momento. Su decisión será aceptada y respetada. No habrá ninguna sanción si decide no participar o dejar de participar.

¿A quién puedo llamar si tengo preguntas o dudas acerca de este estudio de investigación?

Si tiene alguna pregunta acerca de este estudio o de este formulario, consúltenos. Puede llamarnos por preguntas o dudas las veces que desee.

Puede llamar directamente a un miembro del personal del estudio a [redacted].

El Estudiodel Corazón de Framingham es realizado por los investigadores de la Universidad de Boston, el Instituto Nacional Cardíaco, Pulmonar y Sanguíneo, y el Instituto Nacional de la Salud. El [redacted] Se comunicará con una persona del Centro Médico de Boston y de la Junta de Revisión Institucional (*Institutional Review Board*, IRB) del Campus Médico de la Universidad de Boston (Boston University Medical Campus, BUMC). La IRB es un grupo que ayuda a supervisar las investigaciones. Si desea conocer sus derechos como sujeto de una investigación, debe llamar

o enviar un correo electrónico a la IRB. Comuníquese también con esta agencia si desea hablar sobre sus preguntas, inquietudes o problemas con una persona ajena a este estudio.

¿Qué sucederá en este estudio de investigación?

Usted deberá ayunar durante 10 horas antes de llegar a su cita debido a la muestra de sangre que tomaremos. Si toma algún medicamento en la mañana, hágalo como siempre. Puede continuar bebiendo agua durante el ayuno.

Su examen se llevará a cabo en el Centro de Investigación del Estudio del Corazón de Framingham (*Framingham Heart Study*, FHS) en 73 Mount Wayte Avenue, Framingham, MA, por teléfono o videoconferencia (también llamada *teleconsulta*), o en su casa u otra residencia. El examen completo en el lugar tomará alrededor de 4 a 5 horas. También se puede dividir en varias partes: 2 horas por teleconsulta y 2,5 horas por consulta en persona en el Centro de Investigación. Los componentes del examen que puedan completarse a la distancia se incluirán durante la teleconsulta y los que requieran una evaluación en persona se llevarán a cabo en el Centro de Investigación o en su casa u otra residencia.

Como en los exámenes anteriores:

- Tomaremos una muestra de sangre para pruebas genéticas y de laboratorio, para poder comprender mejor los factores de riesgo de enfermedades del corazón y otras enfermedades bajo estudio (por ejemplo, la cantidad y la función de diferentes tipos de colesterol en la sangre). La cantidad total de sangre extraída será alrededor de 80 ml, que son unas 5,4 cucharadas. La extracción de sangre

se realizará poco después de su llegada.
- Recolectaremos una muestra de orina.
- Mediremos su altura, peso y cintura.
- Mediremos la fuerza de agarre.
- Realizaremos un electrocardiograma (ECG).
- Mediremos su presión arterial.
- Actualizaremos su historia clínica.
- Haremos una prueba de la función vascular cardíaca (tonometría) que examina la función cardíaca mediante una ecografía (ecocardiograma) y evalúa la rigidez de los vasos sanguíneos (arterias) mediante el registro de la presión arterial y las formas de onda del flujo.
- Le pediremos que firme un formulario de consentimiento para que nos dé permiso de obtener copias de los expedientes médicos, incluidos los de Medicare. Este formulario será válido hasta que usted lo cancele.
- Lo contactaremos más adelante por correo, correo electrónico o por teléfono (llamada o mensaje de texto) para obtener información adicional o para invitarlo a participar en otros estudios relacionados con el FHS. También puede ser invitado a participar de nuevo a otro de nuestros exámenes.

Encuestas
También le pediremos que llene unos cuestionarios sobre, por ejemplo, la función física, dieta, ejercicio, memoria y estado de ánimo y sus hábitos de estilo de vida, incluyendo si fuma o consume alcohol. Algunos de los cuestionarios ya los ha hecho, otros serán nuevos para usted.

Algunas de sus respuestas se grabarán mediante una grabadora audio-digital. Las grabaciones serán analizadas junto con otra información del estudio. También usaremos las grabaciones para asegurarnos de que sus respuestas estén documentadas correctamente.

Hay algunas nuevas actividades de investigación.

1. Fibroscan: Estamos interesados en mejorar nuestra comprensión sobre los factores que pueden ayudar a predecir el desarrollo de grasa hepática y fibrosis hepática (cicatrización). Para este estudio, se le realizará una prueba llamada Fibroscan. El fibroscan mide la presencia de grasa o cicatrices en el hígado. Se genera un pulso sin dolor en la piel que viaja al hígado y mide su dureza.

   ¿Qué riesgos puedo esperar? Puede haber pequeñas molestias por la aplicación del gel y la presión sobre la piel con la punta del aparato fibroscan. Sin embargo, no hay riesgos conocidos asociados con el fibroscan.

   Hay algunas condiciones que pueden interferir con la capacidad del dispositivo para obtener medidas válidas. Estas incluyen las siguientes: estar embarazada, tener líquido en la cavidad abdominal (ascitis) y tener implantes médicos, como un marcapasos. Le pediremos que nos confirme si tiene alguna de estas condiciones para no realizar el fibroscan.

2. Estudio de evaluación del dolor: Estamos interesados en conocer sobre el dolor que las personas pueden experimentar en su vida diaria y comprender mejor por qué algunas personas sienten dolor y otras no o por qué unas personas sienten más dolor que otras, o por qué algunas personas sienten dolor en más partes del cuerpo que otras. Le haremos algunas preguntas sobre el dolor y evaluaremos su sensibilidad a la presión sobre la piel. Para evaluar su sensibilidad a la presión, se presionará un pequeño

dispositivo contra un músculo del hombro y se medirá cuánta presión se aplica antes de que sienta alguna molestia.

¿Qué riesgos puedo esperar? Aunque es poco común, existe la posibilidad de que se produzca irritación de la piel y enrojecimiento o hematomas durante la prueba. Es posible que aparezcan moretones o molestias por la aplicación del medidor de presión durante la prueba del umbral de dolor por presión o por el inflado del manguito del tensiómetro.

3. Estudio de salud del cerebro: Estamos interesados en encontrar otra forma distinta a la evaluación de las pruebas cognitivas para definir la salud del cerebro. Le pediremos que participe en una serie de pruebas motoras que capturarán la salud de su cerebro, que incluyen pruebas de la visión, audición y función motora. Se le realizará una prueba de ojos (sin dilatación); pruebas de audición (usando un iPad y auriculares); y pruebas de la función física (incluye la evaluación de la velocidad de la marcha en una alfombra electrónica, la evaluación durante la caminata normal y mientras se realiza una tarea mental, como contar, y la evaluación cronometrada de ponerse de pie desde una silla).

   ¿Qué riesgo puedo esperar? No existe ningún riesgo en las pruebas de ojos y audición. La prueba de la marcha tiene un riesgo mínimo de caída. Se tomarán todas las precauciones para evitar que esto ocurra. Un miembro del personal del estudio estará cerca de usted para evitar que se caiga y lo ayudará en caso de ser necesario.

4. Estudio electrónico del FHS (eFHS): Si vive en los Estados Unidos, tiene correo electrónico y acceso diario a Internet o un teléfono inteligente, lo invitamos a participar en el estudio eFHS. Para participar es necesario que ingrese a una plataforma web, descargue las aplicaciones y use dispositivos inalámbricos. Las aplicaciones requieren completar encuestas sobre salud y estilo de vida. Los dispositivos electrónicos miden la frecuencia cardíaca, presión arterial, peso y actividad física.

   ¿Qué riesgos puedo esperar? No existen riesgos conocidos por participar en este estudio.

5. Estudio del hueso: Estamos interesados en conocer cómo cambia el esqueleto con el envejecimiento. Le pediremos que participe en dos pruebas de densidad ósea para examinar la estructura ósea de la parte inferior de la pierna y el antebrazo. Es una prueba no invasiva e indolora y proporciona una imagen detallada de la "microarquitectura" del interior del hueso. Cada una dura aproximadamente dos minutos y requiere que se mantenga lo más quieto posible.

   ¿Qué riesgos puedo esperar? Las pruebas de densidad ósea implican el uso de rayos x, que son una forma de radiación. La dosis de radiación para los dos escaneos juntos será inferior a 10 µSv. Esto equivale a 2 o 3 días de radiación de fondo que experimentan las personas en los Estados Unidos. Debido a que la cantidad de radiación de las pruebas de densidad ósea es muy pequeña, no se conocen efectos a largo plazo en su salud por esta radiación.

Algunos de los componentes del estudio descritos en esta sección "¿Qué sucederá en este estudio de investigación?" no se puede administrar durante la teleconsulta, debido a la necesidad de realizar algunas mediciones en persona. Además, algunos de los exámenes del estudio no se pueden realizar fuera del Centro de Investigación, ni en su casa ni en un centro de atención, debido al tamaño del equipo necesario que imposibilita su traslado. Por ejemplo,

el fibroscan, la tonometría y la tomografía computarizada (TC).

Riesgos y malestares generales del examen
Riesgos generales: Este estudio lleva tiempo y es repetitivo. Otras molestias incluyen dolores de cabeza, sentirse con hambre debido al ayuno, tener fatiga y escalofríos durante la visita.

Las pruebas de densidad ósea por TC implican exposición a radiación. Debido a que la cantidad de radiación es muy pequeña, equivale a 2 o 3 días de radiación de fondo y no se conocen efectos a largo plazo en su salud por esta radiación. Sin embargo, debido al riesgo potencial para un feto, las mujeres embarazadas, según lo determinado por un autoinforme o por una prueba de embarazo positiva, serán excluidas de esta prueba.

No esperamos ningún riesgo de lesiones como resultado de su participación en el estudio. Sin embargo, tenemos disponibles primeros auxilios.

Riesgos desconocidos: Existe la posibilidad de otros riesgos que no hemos identificado hasta el momento.

Estudios genéticos
Es posible que ya haya otorgado su consentimiento para la recolección de muestras biológicas para la investigación del ADN o la creación de células madre con pluripotencialidad inducida (*Induced Pluripotent Stem Cells*, células iPS). Planeamos continuar realizando investigaciones genéticas con el ADN de sus muestras biológicas, las cuáles incluyen células sanguíneas, células de los tejidos, etc. El ADN es el material con el que están hechos sus genes. Los genes pasan del padre y la madre al hijo. Todos los seres vivos están compuestos de células. Los genes son la parte de las células que contienen las instrucciones para decirle a nuestro cuerpo cómo crecer y trabajar, y determinar sus características físicas, como cabello y color de ojos.

También, si está de acuerdo, en un laboratorio, procesaremos las células blancas de la sangre de una de sus muestras para convertirlas en células madre. Las células resultantes son conocidas como *células madre con pluripotencialidad inducida* (células iPS) y se utilizan en el laboratorio para que actúen como células de otros órganos; tales como células del hígado, células grasas, células del corazón, células pulmonares, vasculares, intestinales, células nerviosas, diferentes tipos de células sanguíneas y muchos otros tipos de células naturales. Estas células y los productos celulares que pueden obtenerse de ellas, tales como ARN, proteínas y metabolitos, pueden ser estudiados en laboratorios para aprender más sobre las causas de la salud o enfermedad de estos órganos.

Las células serán guardadas indefinidamente en un repositorio de células madre en la Universidad de Boston. Las células también pueden almacenarse en un repositorio central o banco.

Si está de acuerdo, sus tejidos, células o cualquier línea de células iPS o sus derivados podrían ser usados en el futuro para estudios relacionados y no relacionados, como los siguientes:

- Inyección o trasplante de células madre o sus derivados a animales para fines de investigación. Sus muestras podrían ser usadas en estudios que involucran manipulación genética, pero jamás serán usadas para clonar o reproducir a un ser humano completo.
- Pruebas genéticas y composición del ADN. Los genes pueden ser analizados o manipulados para estudiar su función normal y desarrollo. El ADN de

algunas células madre o sus derivados podría ser alterado.

- Otros usos que implican investigación o desarrollo de productos comerciales para el diagnóstico, prevención o tratamiento de diversas enfermedades.
- Las muestras obtenidas de usted en este estudio (células sanguíneas, células iPS o sus derivados) pueden ser utilizadas en el desarrollo de uno o más productos terapéuticos o de diagnóstico que podrían ser patentadas y autorizadas por los investigadores involucrados en la investigación o en el desarrollo de estos productos. No hay planes para proporcionar compensación económica si esto ocurriera.

¿Cómo puedo saber los resultados de este estudio?

La principal manera en que los resultados de este estudio son reportados es a través de publicaciones científicas y con presentaciones en reuniones científicas. En nuestros boletines informativos y en nuestro sitio web del estudio, a veces también describimos los hallazgos resumidos.

También informaremos los resultados de mediciones rutinarias de investigación a usted o a su proveedor de atención médica en el momento del examen o después de su visita. Estos pueden incluir, por ejemplo, la presión arterial y el colesterol.

En algunos casos, si determinamos que es apropiado, podemos informarlo a usted o a su proveedor de atención médica los hallazgos de investigación que se relacionen con usted si nos da su permiso para ello. Esta información, si se da a conocer, podría tomar mucho tiempo después de su visita por una serie de razones: por ejemplo, podría llevar años de trabajo para analizar la información y llegar a resultados de investigación, quizás utilizando métodos científicos que han sido desarrollados solo recientemente.

Nuestra investigación genética podría generar resultados que sean relevantes para usted y, posiblemente, su familia; tales como información sobre una variante genética en particular que lo pudiera poner en riesgo de una afección de salud grave. Por el momento, pensamos que la mayoría de los hallazgos de investigación genética no tienen gran importancia médica para las personas, pero el campo de la genética está cambiando rápidamente.

Actualmente no tenemos planes concretos de contactarlo a usted o a su proveedor de atención médica sobre los resultados de las diferentes investigaciones genéticas o no genéticas, excepto por las mediciones de pruebas rutinarias de la investigación. En general, no nos podemos comprometer a proporcionarle otros resultados del estudio. En cuanto a determinar si compartimos información adicional de la investigación con usted, tendremos en cuenta una serie de consideraciones, según cada caso en particular. Estos pueden incluir si los hallazgos se basaron en pruebas que son clínicamente aceptables, precisas y fiables, si los resultados revelan un riesgo significativo de una afección de salud grave, si existe en el momento pertinente un tratamiento reconocido o la intervención de prevención u otras acciones disponibles que tienen el potencial para cambiar el curso clínico de la condición de salud, si informar o no informar los resultados pudiera aumentar el riesgo de daño a usted, y otros factores relevantes que quizá no seamos capaces de predecir en este momento. En los casos en que se le informen los hallazgos de la investigación genética, un investigador del estudio y un asesor genético se comunicarán con usted para confirmar su interés continuo en conocer los resultados de la investigación genética. Si confirma su interés, el personal del estudio le

informará sobre los resultados de la investigación y le recomendará los siguientes pasos por seguir, como obtener pruebas clínicas de confirmación y hablar con su proveedor de atención médica personal.

Las mediciones y resultados de una investigación científica no equivalen a los resultados de pruebas clínicas. Como tal, nuestro examen de investigación no se realiza necesariamente por personas calificadas con formación clínica, y muchas partes de la examinación no cumplen con las normas requeridas para pruebas clínicas certificadas. Por esta razón, nuestras pruebas de investigación no son confiables para hacer diagnósticos, tratamientos ni decisiones para planes de salud. No brindamos atención médica, no damos consejos médicos, ni pruebas genéticas, ni brindamos asesoramiento. Si usted o su proveedor de atención médica decide hacer pruebas adicionales de seguimiento o los tratamientos necesarios, usted (o un tercero, como una aseguradora médica o Medicare) será responsable por esos costos.

¿Cómo se comparten mis muestras y mi información con otros investigadores?

Las muestras e información serán guardadas indefinidamente. Si está de acuerdo, sus datos y sangre donada, células de sangre, células iPS o sus derivados, orina y otros especímenes pueden ser compartidos con otros investigadores, incluyendo otras entidades académicas con o sin fines de lucro, como hospitales, universidades, bancos de almacenamiento de células/tejidos y repositorios, bases de datos y repositorios de datos y empresas (ya sea con fines relacionados o no con estudios de investigación). Los bancos de almacenamiento de células/tejidos y repositorios, los bancos de datos y los repositorios de datos incluyen, entre otros, los repositorios de los NIH dbGaP y BioLINCC. Los investigadores internos y externos pueden solicitar datos y materiales para la investigación. Los repositorios tienen procedimientos operativos estándar para proteger su confidencialidad. Ninguna muestra o información será etiquetada con su nombre o ningún otro identificador personal. Solo con códigos.

La información de las grabaciones de audio codificadas será analizada por colaboradores calificados dentro y fuera del BUMC. Su nombre y otros identificadores personales directos no se compartirán con estas entidades.

Usted tiene el derecho de negarse a permitir que sus datos y muestras sean usados o compartidos para futuras investigaciones. Marque la casilla correspondiente en la lista de abajo.

Si usted da su permiso para que sus datos y muestras biológicas sean utilizados o compartidos para futuras investigaciones, usted podrá retirar su autorización en cualquier momento comunicándose con los investigadores del FHS. Sin embargo, si sus datos o muestras ya han sido compartidos con otros investigadores, no podremos instruirles para que dejen de usarlos o destruirlos al igual que con los productos hechos de estas muestras. Sus datos y muestras no incluirán su nombre ni otros identificadores directos.

¿Qué riesgos puedo esperar?

Los riesgos generales y los riesgos individuales relacionados con las nuevas actividades se mencionaron anteriormente.

La participación en la investigación genética podría tener un impacto negativo para usted, su familia y sus seres queridos. Los estudios genéticos podrían producir resultados en la investigación que se relacionen con riesgos a una afección de salud grave u otra información

genética que podríamos considerar apropiado informarle a usted y a su proveedor de atención médica, si es que lo desea (véase abajo). Esto podría presentarle algunas decisiones difíciles respecto a la información disponible y correr el riesgo de saber sobre enfermedades que usted y sus miembros familiares pudieran enfrentar. Saber los resultados de una investigación genética podría ocasionar ansiedad e influir en decisiones relacionadas con el matrimonio, la planificación familiar y otros temas. Existe una pequeña posibilidad de riesgo de que su información genética se utilice en su contra. Por ejemplo, si los hallazgos de la investigación genética sugieren un problema de salud grave, eso podría usarse para dificultarle la tarea de conseguir o mantener un trabajo o un seguro. Tanto las leyes estatales de Massachusetts como las leyes federales, en particular, la *Genetic Information Nondiscrimination Act* [Ley de No Discriminación por Información Genética] (GINA), en general, prohíben que las compañías de seguros médicos, los planes médicos grupales y la mayoría de los empleadores lo discriminen en función de su información genética. Estas leyes, generalmente, lo protegerán de las siguientes maneras:

1. Las compañías de seguros médicos y los planes médicos grupales no pueden solicitar la información genética que obtendremos de esta investigación.
2. Las compañías de seguros médicos y los planes médicos grupales no pueden usar su información genética para tomar decisiones sobre su elegibilidad o primas.
3. Los empleadores de Massachusetts con 6 o más empleados (o 15 o más empleados en otros estados, según la GINA) no pueden usar su información genética que obtendremos de esta investigación para tomar la decisión de contratarlo, ascenderlo o despedirlo o para establecer los términos de su empleo.

Tenga en cuenta que ni la ley de Massachusetts ni la GINA lo protegen contra la discriminación genética por parte de compañías que venden seguros de vida, seguros por discapacidad o seguros de atención a largo plazo. Por lo tanto, las compañías de seguros de vida, de discapacidad y de atención a largo plazo pueden preguntarle legalmente si se ha sometido a pruebas genéticas y negarle la cobertura si usted se niega a responderles.

¿Qué tan protegida está mi información?

Almacenaremos su información de formas que consideremos seguras. Etiquetaremos sus muestras e información con un código y mantendremos las claves de los códigos en una base de datos protegida con contraseña. Solo al personal autorizado se le da la contraseña. Usaremos otros medios seguros en nuestras instalaciones y en nuestra tecnología y sistemas de información para proteger su privacidad y su información.

No vendemos, rentamos ni arrendamos su información de contacto.

Su nombre y otros identificadores personales directos no se usarán cuando la información de este estudio es publicada o presentada en reuniones científicas, ni cuando sus muestras o información se comparten con otros investigadores, ni cuando las guardamos en repositorios y bancos de muestras y datos.

Sin embargo, no garantizamos la privacidad total. Nosotros podemos dar acceso a su información para realizar el estudio y para asegurarnos de que hacemos el estudio, según las normas establecidas por la ética, el derecho y los grupos de calidad. La información puede ponerse a disposición de los investigadores que forman parte de este estudio, pero también de la Junta de Revisión Institucional que dirige esta investigación, de empleados y organizaciones que necesitan la información para hacer su trabajo en la realización y supervisión del estudio, personas o grupos que nos contratan para trabajar para nosotros (como empresas de almacenamiento de datos de muestras biológicas, compañías de seguros y abogados) y

organismos federales y estatales, según lo exija la ley o si están implicados en la investigación o supervisión de nuestro estudio. En la mayoría de los casos, cualquier información que se da es identificada con códigos y no con su nombre u otros identificadores personales directos. Una vez que se da información a terceros, no podemos prometer que se mantendrá en privado. Tenga en cuenta que su información personal puede ponerse a disposición si es requerida por la ley (como, por ejemplo, para evitar posibles lesiones a usted o a otros).

Este estudio está cubierto por un certificado de confidencialidad (*Certificate of Confidentiality*, CoC) de los Institutos Nacionales de Salud. Todos los estudios financiados por los Institutos Nacionales de Salud que involucran información identificable o muestras biológicas están cubiertos por un CoC. El CoC determina cómo podemos compartir información de investigación o muestras biológicas. Debido a que tenemos un CoC, no podemos entregar información de investigación o muestras biológicas que puedan identificarlo a ninguna persona que no participe en la investigación, excepto como se describe a continuación. Aunque una persona intentara obtener su información o muestras biológicas para un procedimiento legal, no podemos dársela. El CoC no le impide compartir su propia información de investigación.

Si usted acepta participar en el estudio y firmar este formulario, compartiremos información y muestras biológicas que puedan revelar su identidad con los siguientes grupos de personas:

- Personas que realizan la investigación o ayudan a supervisar la investigación, incluso el control de seguridad.
- Personas de agencias federales y estatales que auditan o revisan la investigación, según lo exige la ley. Dichas agencias pueden incluir las siguientes: el Departamento de Salud y Servicios Sociales de EE. UU., la Administración de Alimentos y Medicamentos, los Institutos Nacionales de Salud y el Departamento de Salud Pública de Massachusetts.
- Los investigadores que obtendrán sus datos y muestras biológicas, según detallamos en la sección "¿Qué sucederá en este estudio de investigación?". Se espera que estas personas protejan su información y muestras biológicas de la misma manera en la que las protegemos nosotros.

- Cualquier persona para la que usted nos haya dado permiso por separado para compartir su información.

Debe saber que estamos obligados a informar sobre abuso o negligencia infantil, maltrato a personas mayores, enfermedades de notificación específicas o daños a otras personas.

Compartiremos los datos de la investigación una vez que hayamos eliminado cualquier cosa que consideremos que podría revelar su identidad. De todas maneras, podría haber una pequeña posibilidad de que alguien pueda averiguar que la información es acerca de usted. Dicha divulgación incluye lo siguiente:

- La publicación de los resultados en revistas o libros médicos.
- La incorporación de los resultados a una base de datos del Gobierno federal.
- El uso de los datos de la investigación en estudios futuros, realizados por nosotros o por otros científicos.
- El uso de las muestras biológicas en estudios futuros, realizados por nosotros o por otros científicos.

Las muestras que se obtengan de usted en este estudio se analizarán para averiguar información sobre su composición genética. Es posible que su información genética y de salud,

sin su nombre ni ningún otro dato que pudiera identificarlo fácilmente, se incluya en una base de datos administrada por los Institutos Nacionales de la Salud (NIH). Esto podría incluir la información completa de su genoma. Otros investigadores pueden solicitarles a los NIH su información de la base de datos. Debe saber que es posible que su información genética podría utilizarse para identificarlos a usted o a su familia, aunque creemos que no es demasiado probable que esto suceda. Una vez que su información se entregue a la base de datos de los NIH, puede solicitar que los NIH dejen de compartirla, pero no podrá recuperar información que ya fue entregada.

Patentes de descubrimientos

Algún día, la investigación de este estudio resultará en nuevas pruebas para diagnosticar o predecir enfermedades. También puede llevar al desarrollo de nuevas formas de prevenir o tratar enfermedades. Como es el caso de todas las investigaciones financiadas por el Gobierno federal, los investigadores y sus empleadores tienen permitido, por la Ley Federal de Patentes de Descubrimientos, beneficiarse financieramente. Ni usted ni sus herederos se beneficiarán financieramente.

¿Cuáles son los posibles beneficios de mi participación en este estudio?

A usted no se le pagará por participar en el estudio ni obtendrá beneficios médicos como resultado de su participación. Sin embargo, esperamos que este estudio nos ayude a comprender mejor qué es lo que causa enfermedades del corazón y otras enfermedades y afecciones, así como las mejores maneras de prevenir y tratar estas enfermedades.

¿Cuáles son los costos por participar en el estudio?

Los costos que pudiera incurrir el día de su participación incluyen, entre otros, costos de transporte (gasolina, peajes, etc.) y el no poder trabajar el tiempo que esté aquí.

Usted no recibirá ningún pago por participar en este estudio.

El Estudio del Corazón de Framingham no hará arreglos especiales de compensación o pago por su participación en este estudio. Si piensa que ha sufrido una lesión por participar en este estudio, comuníqueselo de inmediato al investigador. La Universidad de Boston y los patrocinadores del estudio, no ofrecen un programa de compensación debido al costo por la atención médica que pudiera recibir si sufriera lesiones, discapacidad, dolor, malestar u otros gastos, como pérdida de salario. Si sufriera lesiones aquí y si su seguro médico no cubriera su atención médica, no le compensaremos por el gasto de la atención médica que reciba. Esto no lo hace renunciar a ninguno de sus derechos legales.

¿Cuánto tiempo estaré en el estudio?

El Estudio del Corazón de Framingham es un estudio a largo plazo.

La participación en este estudio depende solo de usted. Puede optar por participar o por no participar. Si ahora decide participar, puede cambiar de opinión y dejar de hacerlo más adelante.

Le haremos saber si encontramos información nueva que pudiera hacerlo cambiar de parecer respecto a su participación en este estudio.

El investigador puede decidir interrumpir su participación sin su autorización debido a que este considera que su continuidad en el estudio podría ser perjudicial para usted o el patrocinador puede suspender el estudio.

Lea las siguientes afirmaciones y marque la casilla apropiada abajo:

1) Estoy de acuerdo en participar en el examen del FHS, que incluye la recolección de datos, muestras de sangre, orina y varias pruebas de investigación y mediciones. Estoy de acuerdo en que se usen mis datos, muestras y materiales de investigación para los estudios de factores que contribuyen a enfermedades del corazón, los vasos sanguíneos, los pulmones y la sangre, accidentes cerebrovasculares, pérdida de memoria, cáncer y otras enfermedades y afecciones de salud.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 0*)

2) Estoy de acuerdo en permitir que mis datos, sangre, ADN y otro material genético, células iPS y sus derivados, muestras de orina y otros especímenes, sean utilizados en la investigación genética de los factores que contribuyen a enfermedades del corazón, los vasos sanguíneos, los pulmones y la sangre, accidentes cerebrovasculares, pérdida de memoria, cáncer y otras enfermedades y condiciones de salud.

   | _| SÍ | _| NO (*Para uso interno: código de oficina* 3)

3) Estoy de acuerdo en permitir que investigadores de empresas comerciales tengan acceso a mis datos, sangre, ADN y otro material genético, células iPS y sus derivados, muestras de orina y otros especímenes para investigación. Entiendo que mis datos y muestras se compartirán sin mi nombre o identificadores personales directos.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 4*)

4) Estoy de acuerdo en permitir que el FHS divulgue los resultados de los exámenes y las pruebas de investigación no-genéticas conmigo, mi médico, clínica, hospital u otro proveedor de atención médica.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 30*)

5) Estoy de acuerdo en permitir que el FHS me dé, y con mi permiso también a mi médico, clínica, hospital u otro proveedor de atención médica, información relacionada con la investigación genética referente a mí.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 31*)

Sujeto:_____
Nombre en letra de imprenta del sujeto

Al firmar este formulario de consentimiento, usted indica lo siguiente:

- Que ha leído este formulario (o se lo han leído).
- Que sus preguntas se han respondido a su entera satisfacción.
- Que usted acepta participar voluntariamente en este estudio de investigación.
- Que usted permite el uso y la divulgación de información que pueda identificarlo, según lo explicado, incluso su información de salud.

Para ser completado por el sujeto si firma personalmente

_____ _____
Firma del sujeto Fecha

Para ser completado por el representante legalmente autorizado (Legally Authorized Representative, LAR) si el sujeto no firma personalmente
Doy mi consentimiento en nombre del sujeto.

_____ _____
Nombre en letra de imprenta del representante legalmente autorizado (LAR) Relación con el sujeto

_____ _____
Firma del representante legalmente autorizado Fecha

Investigador:_____
Nombre en letra de imprenta de la persona a cargo del análisis del consentimiento

Para ser completado por el investigador si el sujeto firma personalmente
He explicado personalmente la investigación al sujeto mencionado anteriormente y he respondido todas sus preguntas. Considero que el sujeto comprende lo que implica el estudio y acepta libremente participar.

_____ _____
Firma de la persona a cargo del análisis del consentimiento Fecha

Para ser completado por el investigador si el sujeto no firma personalmente
He explicado personalmente la investigación al representante legalmente autorizado del sujeto mencionado anteriormente y he respondido todas sus preguntas. Considero que el representante legalmente autorizado del sujeto comprende lo que implica el estudio y acepta libremente que el sujeto participe.

Considero que el sujeto mencionado anteriormente (marque una opción):
☐ Es capaz de comprender lo que implica el estudio y acepta libremente participar.
☐ No es capaz de comprender lo que implica el estudio.

_____ _____
Firma de la persona a cargo del análisis del consentimiento Fecha

Framingham Heart Study
Offspring Exam 10, Omni 1 Exam 5
RESEARCH CONSENT FORM

Welcome Back to the Framingham Heart Study

Together we are helping to fight heart disease and other major diseases and health conditions through research.

Basic Information

Title of Project: Framingham Heart Study

IRB Number: H-32132

Sponsor: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)

Principal Investigator: Vasan S. Ramachandran, MD
fhs@bu.edu
73 Mount Wayte Avenue, Suite 2
Framingham, MA 01702

Study Phone Number: (508) 872-6562 or (800) 854-7582

PI Phone Number: (617) 358-1310 for Dr. Vasan S. Ramachandran

Why is the research study being done?

The Framingham Heart Study is a long-term research study. The purpose of the study is:

(1) To help understand how heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other major diseases and health conditions develop; and

(2) To examine DNA and its relationship to the risks of developing these diseases and other health conditions.

The research examination that will be conducted as part of this study is not clinical care. The tests are for research purposes only. We do not provide medical services. This research examination does not take the place of medical care by your own health care provider.

About your consent

Please read this research consent form carefully. It tells you important information about the research study. Taking part in a research study is voluntary. The decision whether or not to take part in all or any part of the research exam is entirely up to you. If you choose to take part, you

can decide to stop at any time. Your decision will be honored and respected. There will be no penalty to you if you decide to stop or not to take part.

If I have questions or concerns about this research study, whom can I call?

If you have any questions about the research or about this form, please ask us. You can call us with your questions or concerns. You can ask questions as often as you want.

You can call a study staff member directly at [redacted]

The Framingham Heart Study is led by investigators from Boston University and the National, Heart, Lung, and Blood Institute at the National Institutes of Health. Dr. Vasan S Ramachandran and Dr. Daniel Levy are in charge of the research study. You can contact [redacted]

[redacted] You will be talking to someone at the Boston Medical Center and Boston University Medical Campus IRB. The IRB is a group that helps monitor research. You should call or email the IRB if you want to find out about your rights as a research subject. You should also call or email if you want to talk to someone who is not part of the study about your questions, concerns, or problems.

What will happen in this research study?

You will need to fast for 10 hours before you come to the study appointment for the blood draw. You can continue to drink water while fasting and take your usual medication on the morning of your visit.

Your research examination will take place at the FHS Research Center at 73 Mount Wayte Avenue, Framingham, MA, by phone or video conference (also referred to as a televisit), or in your home or other residence. The full onsite research exam will take around 4-5 hours to complete or the exam may also be split into multiple pieces: a 2-hour televisit and 2.5 hour in-person visit at the Research Center. Exam components that may be completed remotely will be included during the televisit and components that require in-person assessment will be conducted at the Research Center or offsite home or other residence.

As before, we will

- draw a sample of blood for genetic and laboratory tests to better understand risk factors for heart disease and other diseases under investigation (for example, the amount and function of different types of cholesterol in your blood). The total blood draw will be up to 80mL, which is about 5.4 tablespoons. The blood draw will occur soon after your arrival.
- collect a urine sample
- measure your height, weight, and waist
- measure grip strength
- complete an electrocardiogram (ECG)
- record your blood pressure
- update your medical history information

- complete a test of cardiac vascular function (tonometry) that examines heart function using ultrasound scanning (echocardiogram) and tests blood vessel (artery) stiffness by recording the blood pressure and flow waveforms
- ask you to sign a form to allow FHS to obtain copies of medical records, including Medicare records. The release form is valid to obtain these records unless canceled by you.
- contact you later by mail, email, or by phone (call or text) to obtain additional information or to invite you to participate in further FHS related studies. You may also be invited to return for another examination in the future.

Surveys
We will also be asking you to complete questionnaires such as physical function, diet, exercise, memory and mood, and your lifestyle habits, including whether you smoke or use alcohol. Some of the questionnaires you will have seen before and others will be new to you.

Some of your responses will be recorded using a digital audio recorder. Recordings will be analyzed in conjunction with other study information. We will also use recordings to make sure that your responses are accurately documented.

There are some new research activities.

1. Fibroscan: We are interested in improving our understanding of the factors that can help predict the development of liver fat and liver fibrosis (scarring) for this study, you will have a test called a Fibroscan. The Fibroscan measures the presence of fat or scarring in the liver. A painless pulse is generated on your skin that travels to the liver and measures how stiff your liver is.

   What risks can I expect? There may be minor discomfort from the application of lubricating jelly and pressure on the skin from the Fibroscan probe. However, there are no known risks associated with the Fibroscan.

   There are some conditions that may interfere with the ability of the device to obtain valid measures. They include being pregnant, having fluid in the abdominal cavity (ascites), and having implanted medical devices, such as a heart pacemaker. We will ask you to confirm if you have any of these conditions and if you do, we will not complete the Fibroscan.

2. Pain Assessment Study: We are interested in learning about pain people may be experiencing in their daily lives, and to better understand why some people have pain, more pain, or pain in more parts of their body, than other people do. We will ask some questions about pain and assess your sensitivity to pressure on your skin. To test your sensitivity to pressure, a small device will be pressed against a muscle on your shoulder to measure how much pressure is applied before you feel any discomfort.

   What risks can I expect? Although rare, there is the potential for skin irritation and redness or bruising during testing. Bruising or discomfort could potentially result from application of the pressure meter during pressure pain threshold testing and/or blood pressure cuff inflation.

3. Brain Health Study: We are interested in finding a way to define brain health beyond the evaluation of cognitive testing. We will ask you to participate in a number of sensory

motor tests that capture your brain health, including testing your vision, hearing, and motor function. You will have eye testing (without dilatation); hearing testing (using an iPad and headphones); and physical function testing (includes gait speed assessment on an electronic gait mat, during normal walk and while doing a mental task like counting and timed chair stands).

What risk can I expect? There are no risks involved in eye and hearing testing. Gait testing has a minimal risk of falling. All precautions will be taken to prevent falls. A study staff member will stand near you to prevent you from falling and help you if needed.

4. Electronic FHS (eFHS) Study: If you live in the US, have an email account with access to a daily Internet connection or have a smartphone, we will invite you to take part in the eFHS study. Taking part requires that you visit a web platform, download apps and use wireless devices. The apps will require you to complete surveys regarding lifestyle and health, and the devices will measure heart rate, blood pressure, weight, and physical activity.

   What risks can I expect? There are no known risks to taking part in this study.

5. Bone Scan: We are interested in learning about how the skeleton changes with aging. We will ask you to participate in two bone scans to examine the bone structure in your lower leg and lower arm. The scan is a non-invasive and painless test, and provides a detailed image of the "micro-architecture" inside the bone. Each scan takes about two minutes and requires that you keep as still as possible.

   What risks can I expect? Bone scans involve the use of x-rays, a form of energy also called radiation. The radiation dose for the two scans together will be less than 10 μSv, which is equivalent to 2-3 days of background radiation that individuals experience in the U.S. Since the amount of radiation from the bone scans is so small, there are no known long-term effects of this radiation on your health.

Some of the study components described in this section "What will happen in this research study?" may not be administered during televisits, due to the need to take certain measurements in person. Also, some of the study components may not be administered during offsite examinations taking place at your home or care facility, due to large equipment that cannot be transported outside of the research center. For example, Fibroscan, Tonometry, and Computed Tomography.

Overall Examination Risks and Discomforts
General Risks: The research exam is time consuming and repetitive. Other discomforts include headaches, feeling hungry due to fasting, fatigue and chill during the visit.

CT bone scans involve exposure to radiation. Since the amount of radiation is so small, equivalent to 2-3 days of background radiation there are no known long-term effects of this radiation on your health. However due to potential risk to a fetus, pregnant women, as determined by self-report or by a positive pregnancy test, will be excluded from this test.

We do not expect any risk of injury as a result of your participation in the study. However, first aid will be available.
Unknown Risks: There may also be some risks that we are unable to determine at this time.

Genetic Studies

You may have already provided consent for the collection of biological samples for DNA research or the creation of Induced Pluripotent Stem Cells (iPS cells). We plan to continue to do genetic research on the DNA from your biological samples. The biological samples include blood cells, tissue cells, etc. DNA is the material that makes up your genes. Genes are passed from parent to child. All living things are made of cells. Genes are the part of cells that contain the instructions which tell our bodies how to grow and work and determine physical characteristics such as hair and eye color.

Also, if you agree, we will process white blood cells from a sample of your blood to become stem cells in the laboratory. The resulting cells are known as Induced Pluripotent Stem Cells (iPS cells), and they will be used in the laboratory to act like cells from other organs, such as liver cells, fat cells, heart cells, lung cells, vascular cells, gut cells, nerve cells, different types of blood cells, and many other engineered or naturally occurring cell types. These cells and the cell products that can be obtained from them such as RNA, proteins, and metabolites may be studied in laboratories to learn more about the causes of health and diseases of these organs.

Your cells will be stored indefinitely in a stem cell repository at Boston University. Your cells may also be stored in a central repository or bank.

If you agree, your stored tissues, cells and any resulting iPS cell lines or their derivatives could be used in future related and unrelated research studies including:

- Injecting or transplanting the stem cells or their derivatives into animals for research purposes. Your samples may be used in research that involves genetic manipulation but they will not be used to clone or to otherwise create an entire human being.
- Testing for genetic and DNA composition. Genes may be analyzed and/or manipulated to study normal function or development, and some of the DNA in the stem cells or their derivatives may be altered.
- Other uses involving research or development of commercial products for the diagnosis, prevention, or treatment of various diseases.
- Samples (blood cells, the iPS cells, or their derivatives) obtained from you in this study may be used in the development of one or more diagnostic or therapeutic products which could be patented and licensed by those involved in the research or development of such products. There are no plans to provide financial compensation to you should this occur.

How will I learn the results of this study?

The main way results of research from this study are reported is in scientific publications and presentations at scientific meetings. Summary findings are also sometimes described in our newsletters and on our study website.

We will also report some routine research test measurements to you and/or your health care provider at the time of the exam or after your visit. These may include, for example, blood pressure and cholesterol.

In some cases, if we determine it to be appropriate, we may report to you and/or your health care provider research findings as they relate to you, if you give your permission. This information, if it is reported, might be reported long after your visit for a number of reasons. As an example, it might take years of work to analyze information and arrive at research findings, possibly using newly developed scientific methods.
Our genetic research might generate findings that could be relevant to you and possibly your family members, such as information about a particular genetic variant that might put you at risk of a serious health condition. At this time, we believe that most of the genetic research findings do not have medical importance to individuals, but the field of genetics is changing rapidly.

We currently do not have specific plans to contact you or your health care provider about genetic or non-genetic research findings other than some routine research test measurements. In general, we cannot commit to providing any other research findings to you. In determining whether we share additional research information with you, we will take into account a number of considerations on a case-by-case basis. These might include whether the findings were based on tests that are clinically acceptable, accurate and reliable, whether the findings reveal a significant risk of a serious health condition, whether there is, at the relevant time, a recognized treatment or prevention intervention or other available actions that have the potential to change the clinical course of the health condition, whether reporting or not reporting the results is likely to increase the risk of harm to you, and other relevant factors that we might not be able to predict at this time. In the cases when genetic research findings are reported to you, a study investigator and genetic counselor will contact you to confirm your continued interest in hearing about genetic research results. If you confirm your interest, the study staff will inform you of the research results and recommend next steps such as obtaining confirmatory clinical testing and speaking with your personal healthcare provider.

Research test measurements and findings are not the same as clinical test results. As such, our research examination is not necessarily performed by individuals with clinical training and qualifications, and many parts of the examination do not meet the standards for certified clinical testing. For these reasons, our research tests should not be relied on to make any diagnosis, treatment, or health planning decisions. We do not provide health care or give medical advice or genetic testing or provide counseling. If you or your health care provider decides that follow-up tests or treatments are necessary, then you (or a third party such as a health insurance carrier or Medicare) will be responsible for the cost.

How are my samples and information shared with other researchers?

Samples and information will be kept indefinitely. If you agree, your data and donated blood, blood cells, resulting iPS cells or their derivatives, urine, and any other specimens may be shared with other researchers. These include other academic, non-profit, and for-profit entities, including but not limited to hospitals, universities, cell/tissue storage banks and repositories, databanks and data repositories and businesses, whether for related or unrelated research studies. The cell/tissue storage banks and repositories, databanks and data repositories, include but are not limited to, NIH repositories dbGaP and BioLINCC. Internal and external researchers may request data and materials for research. The repositories have standard operating procedures to protect your confidentiality. Your data and samples will not be labeled with your name or other direct personal identifiers, only a code.

Coded audio recording information will be analyzed by qualifying collaborators inside and outside of BUMC. Your name and other direct personal identifiers will not be shared with these entities.

You have the right to refuse to allow your data and samples to be used or shared for further research. Please check the appropriate box in the selection below.

If you give your permission to allow your data and biological samples to be used or shared for further research, you may withdraw your permission at any time by contacting the FHS investigators. However, if your data or samples have already been released to other researchers, we will not be able to instruct the other researchers to stop using them, to destroy them or products made from them. Your data and samples will not include your name or other direct identifiers.

What risks can I expect?

General risks and individual risks related to new activities are discussed above.

Participating in genetic research could have a negative impact on you, your family, and your loved ones. The genetic studies might result in research findings that relate to your risk of a serious health condition or other genetic information that we might consider to be appropriate to report to you and your health care provider, if you wish us to report them (see below). This could present you with some difficult decisions regarding the available information and the disease risks you and your family members might face. Knowledge of genetic research findings can provoke anxiety and influence decisions regarding marriage, family planning, and other matters. There is a potential risk that your genetic information could be used to your disadvantage. For example, if genetic research findings suggest a serious health problem, that could be used to make it harder for you to get or keep a job or insurance. Both Massachusetts state laws and federal laws, particularly the Genetic Information Nondiscrimination Act (GINA), generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. These laws will generally protect you in the following ways:

1. Health insurance companies and group health plans may not request your genetic information that we get from this research.
2. Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
3. Massachusetts employers with 6 or more employees (or 15 or more employees in other states, under GINA) may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that neither Massachusetts law nor GINA protects you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Thus, life insurance, disability insurance, and long-term care insurance companies may legally ask whether you have had genetic testing and deny coverage for refusal to answer this question.

How is my information protected?

We will store your information in ways we think are secure. We label your samples and information with a code, and we keep the key to the code in a password protected database.

Only approved staff is given the password. We use other safeguards at our facilities and for our information technology and systems to protect the privacy and security of your information.

We do not sell, rent, or lease your contact information.

If information from this study is published or presented at scientific meetings, and when your samples and information are shared with other researchers and deposited in data and specimen banks and repositories, your name and other direct personal identifiers will not be used.

However, we cannot guarantee total privacy. We may provide access to your information in order to do the study and to make sure we do the study according to certain standards set by ethics, law, and quality groups. Information may be made available to researchers that are part of this study, the Institutional Review Board that oversees this research, research and non-research staff and organizations who need the information to do their jobs for the conduct and oversight of the study, people or groups that we hire to do work for us (such as data or biosample storage companies, insurers, and lawyers), and Federal and state agencies as required by law or if they are involved in the research or its oversight. In most cases, any information that is given out to others is identified by code and not with your name or other direct personal identifiers. Once information is given to outside parties, we cannot promise that it will be kept private. Please be aware that your personal information may be given out if required by law (e.g., to prevent possible injury to yourself or others).

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. All studies funded by the National Institutes of Health that involve identifiable information or biological samples are covered by a CoC. The CoC provides how we can share research information or biological samples. Because we have a CoC, we cannot give out research information or biological samples that may identify you to anyone that is not involved in the research except as we describe below. Even if someone tries to get your information or biological samples in connection with a legal proceeding, we cannot give it to them. The CoC does not prevent you from sharing your own research information.

If you agree to be in the study and sign this form, we will share information and biological samples that may show your identity with the following groups of people:

- People who do the research or help oversee the research, including safety monitoring.
- People from Federal and state agencies who audit or review the research, as required by law. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health.
- Investigators who will get your data and your biological samples as we described in the section "*What will happen in this research study?"* These people are expected to protect your information and biological samples in the same way we protect it.
- Any people who you give us separate permission to share your information.

You should know that we are required to report information about child abuse or neglect; elder abuse; specific reportable diseases; or harm to others.

We will share research data where we have removed anything that we think would show your identity. There still may be a small chance that someone could figure out that the information is about you. Such sharing includes:

- Publishing results in a medical book or journal.

- Adding results to a Federal government database
- Using research data in future studies, done by us or by other scientists.
- Using biological samples in future studies, done by us or by other scientists.

Samples that are collected from you in this study will be analyzed to find out information about your genetic makeup. Your genetics and health information, without your name or other data that could easily identify you, will be put in a database run by the National Institutes of Health (NIH). This may include your whole genome information. Other researchers can ask the NIH to get your information from the database. You should know that it is possible that your genetics information might be used to identify you or your family, though we believe it is not too likely that this will happen. Once your information is given to the NIH database, you can ask to have NIH stop sharing it, but NIH cannot take back information that was already shared.

Patenting Discoveries

Research from this study may, one day, result in new tests to diagnose or predict diseases. It may also lead to the development of new ways to prevent or treat diseases. As is true of all federally-funded research, researchers and their employers are permitted by Federal law to patent discoveries from which they may gain financially. You and your heirs will not benefit financially.

What are the possible benefits from being in this research study?

While you will not receive any direct benefit as a result of your participation in this study; we hope that this study will help us better understand what causes heart disease and other diseases and conditions and how to better prevent and treat them.

What are the costs of taking part in the study?

Costs that you may incur on the day of your participation include, but are not limited to, loss of work and transportation costs (gas, tolls, etc.).

You will not be paid for your participation in this study.

No special arrangement will be made by the Framingham Heart Study for compensation or payment solely because of your participation in this study. If you think you have been injured by being in this study, please let the investigators know right away. Boston University and the sponsors do not offer a program to provide compensation for the cost of care for research related injury or other expenses such as lost wages, disability, pain, or discomfort. You will be sent a bill for the medical care you receive for research injury if your medical insurance does not pay for your medical care. This does not waive any of your legal rights.

How long will I be in the study?

FHS is a long-term study.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

The investigator may decide to discontinue your participation without your permission because he/she may decide that staying in the study will be bad for you, or the sponsor may stop the study.

Please read the following statements and check the appropriate box below:

1) I agree to participate in the FHS examination, including the collection of data, blood, urine samples, and various research tests and measurements. I agree to the use of all data, samples, and research materials for studies of the factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other diseases and health conditions.

   | _| YES | _| NO (*For Internal Use - Office Code 0*)

2) I agree to allow my data, blood, DNA and other genetic material, iPS cells and their derivatives, urine samples, and any other specimens to be used in genetic research, of factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other diseases and health conditions.

   | _| YES | _| NO (*For Internal Use - Office Code* 3)

3) I agree to allow researchers from commercial companies to have access to my data, blood, DNA and other genetic material, iPS cells and their derivatives, urine samples, and any other specimens for research. I understand that my data and specimens will be shared without my name or direct personal identifiers.

   | _| YES | _| NO (*For Internal Use - Office Code 4*)

4) I agree to allow the FHS to release the findings of non-genetic research tests and examinations to me and/or my physician, clinic, hospital, or other health care provider.

   | _| YES | _| NO (*For Internal Use - Office Code 30*)

5) I agree to allow the FHS to provide me, and with my permission, my physician, clinic, hospital, or other health care provider information relating to genetic research findings as they may relate to me.

   | _| YES | _| NO (*For Internal Use - Office Code 31*)

Subject: _____
Printed name of subject

By signing this consent form, you are indicating that

- you have read this form (or it has been read to you)
- your questions have been answered to your satisfaction
- you voluntarily agree to participate in this research study
- you permit the use and sharing of information that may identify you as described, including your health information.

To be completed by subject if personally signing

_____ _____
Signature of subject Date

To be completed by LAR if subject does not personally sign
I am providing consent on behalf of the subject.

_____ _____
Printed name of Legally Authorized Representative (LAR) Relationship to Subject

_____ _____
Signature of Legally Authorized Representative Date

Researcher: _____
Printed name of person conducting consent discussion

To be completed by researcher if subject personally signs
I have personally explained the research to the above-named subject and answered all questions. I believe that the subject understands what is involved in the study and freely agrees to participate.

_____ _____
Signature of person conducting consent discussion Date

To be completed by researcher if subject does not personally sign
I have personally explained the research to the above-named subject's Legally Authorized Representative and answered all questions. I believe that the Legally Authorized Representative understands what is involved in the study and freely agrees to have the subject participate.

I consider that the above-named subject (check one):
☐ is capable of understanding what is involved in the study and freely agrees to participate.
☐ is not capable of understanding what is involved in the study.

_____ _____
Signature of person conducting consent discussion Date

Framingham Heart Study
Offspring Exam 10, Omni 1 Exam 5
Brain Health Study

RESEARCH CONSENT FORM ADDENDUM

Basic Information

Title of Project: Multidimensional Assessment of Brain Health as a Marker of Dementia Risk and Resilience

IRB Number: H-40757

Sponsor: National Institute on Aging (NIA), National Institutes of Health (NIH)

Principal Investigator: Sudha Seshadri, MD [redacted]

Please take time to review this information carefully. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Voluntary Participation - You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are entitled.

The PI of the Brian Health Study is Dr. Sudha Seshadri who is Professor of Neurology at the University of Texas Health Sciences Center, San Antonio, TX and also an adjunct Professor of Neurology at Boston University School of Medicine. The Program Manager supervising this effort at the Framingham Heart Study site is Mr. Timothy Kowalczyk and the PI of the Framingham site for this study is Dr. Vasan Ramachandran, MD who is also the PI of the overall Framingham Heart Study.

Study Phone Number: 857-389-2359 (Dr. Seshadri)
508-935-3410 (Study Manager, Timothy Kowalczyk)

Overview of the Brain Health Study
We are interested in finding a way to define brain health beyond the evaluation of cognitive testing. We will ask you to participate in a number of sensory motor tests that capture your brain health, including testing your vision, hearing, and motor function. You will have eye testing (without dilatation); hearing testing (using an iPad and headphones); and motor function testing (includes gait speed assessment on an electronic gait mat, during normal walk and while doing a mental task like counting.) As described in the main consent form, we may also report some routine research test measurements to you and/or your health care provider at the time of the exam or after your exam

The Brain Health Study within the Framingham Heart Study Offspring Exam 10, Omni 1 Exam 5 is conducted in collaboration with The University of Texas Health Science Center at San Antonio.

All procedures described below will be performed for research purposes only.
A. Vision Testing:

Optical Coherence Tomography Angiography (OCTA):
This exam will be performed without dilating eye drops. You will be asked to rest your chin and forehead on a support that is attached to the OCT machine. You will be asked to fixate your eyes on a target for a few moments and as a camera scans and takes images of the retina, the back of your eye. It also measures blood flow in the eye and is a completely non-invasive measurement that is approved by the U.S. Food and Drug Administration (FDA) as a rapid method of assessing retinal capillary density

B. **Motor Testing**

In ***Gait Testing***, you will be asked to walk on a gait mat (that appears like a regular rug or mat) that has pressure sensors below it. A computer and software connected to the mat will capture the different aspects of the walk including speed, step length, step width, etc. You will be asked to walk at your usual pace, fast pace and while doing cognitive tasks like counting backwards.

C. Hearing Testing
Using a portable tablet-based system and earphones we will present a **pure tone** to the **ear** measuring the lowest intensity in decibels (dB) at which this **tone** is perceived 50% of the time. This measurement is called **threshold**.

Risks of Participation in this research

Informational risks related to the study
Your data will be assigned a code number. Your name, medical record number, or other information that easily identifies you will not be stored with your samples or data. The key that links your identifying information to the code number will be stored securely in a separate file and will not be shared with researchers that are not part of our study team.
The main risk of allowing us to use your data for research is a potential loss of privacy. This risk is serious but rare because we take many steps to protect your information. We protect your privacy by coding your data and removing personal identifiers. Research results obtained in this study will not be placed in your medical record unless we contact you with a finding of high medical importance. We do not think that there will be further risks to your privacy by sharing your data with other researchers; however, we cannot predict how this data will be used in the future.

Risks of Study Procedures
There is also minimal risk of falling during the gait testing, but we will take the same precautions described above to prevent falls by walking behind and to the side and assisting if required.

For more information about risks and side effects, ask one of the researchers or study staff. We will tell you about any significant new findings which develop during the course of this research which may relate to your willingness to continue taking part.

What if a research-related injury occurs?
The researchers have taken steps to minimize the known or expected risks and we expect no injuries from these studies. However, you may still experience problems or side effects, even though the researchers are careful to avoid them. in the event of a research-related injury or if you experience an adverse reaction, please immediately contact study staff. See the section "Contact Information" for phone numbers and additional information. You may also need to tell your regular doctors.

If you are injured or made sick from taking part in this research study, medical care will be provided. This care may be billed to you or your insurance. Depending on the circumstances, this care may be provided at no cost to you. We do not offer a program to provide compensation for the cost of care for research related injury. The study staff can provide you with more information.

If you sign this form, you do not give up your right to seek additional compensation if you are harmed as a result of being in this study

Information about how this study will use your Protected Health Information (PHI)
Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of monitoring research may want to see study records which identify you as a subject in this study.

Research policies require that private information about you be protected and this is especially true for your health information. However, the law sometimes allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study.

What is Protected Health Information (PHI)?
Protected Health Information is information about a person's health that includes information that would make it possible to figure out who the person is. According to the law, you have the right to decide who can see your protected health information. If you choose to take part in this research study, you will be giving your permission to the investigators and the research study staff (individuals carrying out the study) to see and use your health information for the study. In carrying out this research, the health information we will see and use about you will include:

- your medical history and blood work,
- results of eye, ear and gait assessment tests,
- information from interviews or from questionnaires,
- demographic information like your age, sex

We will get this information from the data collected today and over the years at the Framingham Heart Study

How will your PHI be protected?
In an effort to protect your privacy, the study staff will use code numbers instead of your name, to identify your health information. Initials and numbers will be used on any photocopies of your

study records, and other study materials containing health information that are sent outside the institutions listed above for review or testing. If the results of this study are reported in medical journals or at meetings, you will not be identified.

Parts of your PHI may be photocopied and sent to a central location or it may be transmitted electronically, such as by e-mail, fax, or other secure means of transmission. The groups receiving your health information may not be obligated to keep it private. They may pass information on to other groups or individuals not named here.

How will your PHI be shared with other Researchers?
Because it is research, we will be unable keep your PHI completely confidential. We may share your health information with people and groups involved in conducting and overseeing this research study including:

- the following collaborators at other institutions that are involved with the study: The University of Texas Health Science Center at San Antonio, Boston University School of Medicine, Massachusetts Eye and Ear Infirmary and University of Southern California
- the members of the local research team;
- the Institutional Review Board and the Compliance Office of the University of Texas Health Science Center at San Antonio, and other groups that oversee how research studies are carried out; and
- the Research offices at the University of Texas Health Science Center at San Antonio

If you decide to participate in this study, you will be giving your permission for the groups named above, to collect, use and share your health information for research purposes. If you choose not to let these groups collect, use and share your health information as explained above, you will not be able to participate in this research study.

Do you have to allow the use of your health information?
You do not have to allow (authorize) the researchers and other groups to see and share your health information. If you choose not to let the researchers and other groups use your health information, there will be no penalties, but you will not be allowed to participate in the Brain Health Study portion part of the Framingham Heart Study Examination.

After you enroll in this study, you may ask the researchers to stop using your health information at any time. However, you must provide this in writing and send your letter to ***Vasan Ramachandran, Principal Investigator, Framingham Heart Study, 73 Mt Wayte Ave, Suite 2, Framingham, MA 01702.*** If you tell the researchers to stop using your health information, your participation in this part of the Framingham Heart study will end and the study staff will stop collecting new health information from you and about you for this study. However, the study staff will continue to use the health information collected up to the time they receive your letter asking them to stop.

Can you ask to see the PHI that is collected about you for this study?
The federal rules say that you can see the health information that we collect about you and use in this study. Contact the study staff if you have a need to review your PHI collected for this study. If you ask for research information that is not in your medical record, we might not

Framingham Heart Study
Offspring Exam 10, Omni 1 Exam 5
RESEARCH CONSENT FORM

Welcome Back to the Framingham Heart Study

Together we are helping to fight heart disease and other major diseases and health conditions through research.

Basic Information

Title of Project: Framingham Heart Study

IRB Number: H-32132

Sponsor: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)

Principal Investigator: Vasan S. Ramachandran, MD

[redacted]

Why is the research study being done?

The Framingham Heart Study is a long-term research study. The purpose of the study is:

(1) To help understand how heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other major diseases and health conditions develop; and

(2) To examine DNA and its relationship to the risks of developing these diseases and other health conditions.

The research examination that will be conducted as part of this study is not clinical care. The tests are for research purposes only. We do not provide medical services. This research examination does not take the place of medical care by your own health care provider.

About your consent

Please read this research consent form carefully. It tells you important information about the research study. Taking part in a research study is voluntary. The decision whether or not to take part in all or any part of the research exam is entirely up to you. If you choose to take part, you

can decide to stop at any time. Your decision will be honored and respected. There will be no penalty to you if you decide to stop or not to take part.

If I have questions or concerns about this research study, whom can I call?

If you have any questions about the research or about this form, please ask us. You can call us with your questions or concerns. You can ask questions as often as you want.

You can call [redacted]

[redacted] You will be talking to someone at the Boston Medical Center and Boston University Medical Campus IRB. The IRB is a group that helps monitor research. You should call or email the IRB if you want to find out about your rights as a research subject. You should also call or email if you want to talk to someone who is not part of the study about your questions, concerns, or problems.

What will happen in this research study?

You will need to fast for 10 hours before you come to the study appointment for the blood draw. You can continue to drink water while fasting and take your usual medication on the morning of your visit.

Your research examination will take place at the FHS Research Center at 73 Mount Wayte Avenue, Framingham, MA, by phone or video conference (also referred to as a televisit), or in your home or other residence. The full onsite research exam will take around 4-5 hours to complete or the exam may also be split into multiple pieces: a 2-hour televisit and 2.5 hour in-person visit at the Research Center. Exam components that may be completed remotely will be included during the televisit and components that require in-person assessment will be conducted at the Research Center or offsite home or other residence.

As before, we will

- draw a sample of blood for genetic and laboratory tests to better understand risk factors for heart disease and other diseases under investigation (for example, the amount and function of different types of cholesterol in your blood). The total blood draw will be up to 80mL, which is about 5.4 tablespoons. The blood draw will occur soon after your arrival.
- collect a urine sample
- measure your height, weight, and waist
- measure grip strength
- complete an electrocardiogram (ECG)
- record your blood pressure
- update your medical history information

- complete a test of cardiac vascular function (tonometry) that examines heart function using ultrasound scanning (echocardiogram) and tests blood vessel (artery) stiffness by recording the blood pressure and flow waveforms
- ask you to sign a form to allow FHS to obtain copies of medical records, including Medicare records. The release form is valid to obtain these records unless canceled by you.
- contact you later by mail, email, or by phone (call or text) to obtain additional information or to invite you to participate in further FHS related studies. You may also be invited to return for another examination in the future.

Surveys
We will also be asking you to complete questionnaires such as physical function, diet, exercise, memory and mood, and your lifestyle habits, including whether you smoke or use alcohol. Some of the questionnaires you will have seen before and others will be new to you.

Some of your responses will be recorded using a digital audio recorder. Recordings will be analyzed in conjunction with other study information. We will also use recordings to make sure that your responses are accurately documented.

There are some new research activities.

1. Fibroscan: We are interested in improving our understanding of the factors that can help predict the development of liver fat and liver fibrosis (scarring) for this study, you will have a test called a Fibroscan. The Fibroscan measures the presence of fat or scarring in the liver. A painless pulse is generated on your skin that travels to the liver and measures how stiff your liver is.

   What risks can I expect? There may be minor discomfort from the application of lubricating jelly and pressure on the skin from the Fibroscan probe. However, there are no known risks associated with the Fibroscan.

   There are some conditions that may interfere with the ability of the device to obtain valid measures. They include being pregnant, having fluid in the abdominal cavity (ascites), and having implanted medical devices, such as a heart pacemaker. We will ask you to confirm if you have any of these conditions and if you do, we will not complete the Fibroscan.

2. Pain Assessment Study: We are interested in learning about pain people may be experiencing in their daily lives, and to better understand why some people have pain, more pain, or pain in more parts of their body, than other people do. We will ask some questions about pain and assess your sensitivity to pressure on your skin. To test your sensitivity to pressure, a small device will be pressed against a muscle on your shoulder to measure how much pressure is applied before you feel any discomfort.

   What risks can I expect? Although rare, there is the potential for skin irritation and redness or bruising during testing. Bruising or discomfort could potentially result from application of the pressure meter during pressure pain threshold testing and/or blood pressure cuff inflation.

3. Brain Health Study: We are interested in finding a way to define brain health beyond the evaluation of cognitive testing. We will ask you to participate in a number of sensory

motor tests that capture your brain health, including testing your vision, hearing, and motor function. You will have eye testing (without dilatation); hearing testing (using an iPad and headphones); and physical function testing (includes gait speed assessment on an electronic gait mat, during normal walk and while doing a mental task like counting and timed chair stands).

What risk can I expect? There are no risks involved in eye and hearing testing. Gait testing has a minimal risk of falling. All precautions will be taken to prevent falls. A study staff member will stand near you to prevent you from falling and help you if needed.

4. Electronic FHS (eFHS) Study: If you live in the US, have an email account with access to a daily Internet connection or have a smartphone, we will invite you to take part in the eFHS study. Taking part requires that you visit a web platform, download apps and use wireless devices. The apps will require you to complete surveys regarding lifestyle and health, and the devices will measure heart rate, blood pressure, weight, and physical activity.

   What risks can I expect? There are no known risks to taking part in this study.

5. Bone Scan: We are interested in learning about how the skeleton changes with aging. We will ask you to participate in two bone scans to examine the bone structure in your lower leg and lower arm. The scan is a non-invasive and painless test, and provides a detailed image of the "micro-architecture" inside the bone. Each scan takes about two minutes and requires that you keep as still as possible.

   What risks can I expect? Bone scans involve the use of x-rays, a form of energy also called radiation. The radiation dose for the two scans together will be less than 10 μSv, which is equivalent to 2-3 days of background radiation that individuals experience in the U.S. Since the amount of radiation from the bone scans is so small, there are no known long-term effects of this radiation on your health.

Some of the study components described in this section "What will happen in this research study?" may not be administered during televisits, due to the need to take certain measurements in person. Also, some of the study components may not be administered during offsite examinations taking place at your home or care facility, due to large equipment that cannot be transported outside of the research center. For example, Fibroscan, Tonometry, and Computed Tomography.

Overall Examination Risks and Discomforts
General Risks: The research exam is time consuming and repetitive. Other discomforts include headaches, feeling hungry due to fasting, fatigue and chill during the visit.

CT bone scans involve exposure to radiation. Since the amount of radiation is so small, equivalent to 2-3 days of background radiation there are no known long-term effects of this radiation on your health. However due to potential risk to a fetus, pregnant women, as determined by self-report or by a positive pregnancy test, will be excluded from this test.

We do not expect any risk of injury as a result of your participation in the study. However, first aid will be available.
Unknown Risks: There may also be some risks that we are unable to determine at this time.

Genetic Studies

You may have already provided consent for the collection of biological samples for DNA research or the creation of Induced Pluripotent Stem Cells (iPS cells). We plan to continue to do genetic research on the DNA from your biological samples. The biological samples include blood cells, tissue cells, etc. DNA is the material that makes up your genes. Genes are passed from parent to child. All living things are made of cells. Genes are the part of cells that contain the instructions which tell our bodies how to grow and work and determine physical characteristics such as hair and eye color.

Also, if you agree, we will process white blood cells from a sample of your blood to become stem cells in the laboratory. The resulting cells are known as Induced Pluripotent Stem Cells (iPS cells), and they will be used in the laboratory to act like cells from other organs, such as liver cells, fat cells, heart cells, lung cells, vascular cells, gut cells, nerve cells, different types of blood cells, and many other engineered or naturally occurring cell types. These cells and the cell products that can be obtained from them such as RNA, proteins, and metabolites may be studied in laboratories to learn more about the causes of health and diseases of these organs.

Your cells will be stored indefinitely in a stem cell repository at Boston University. Your cells may also be stored in a central repository or bank.

If you agree, your stored tissues, cells and any resulting iPS cell lines or their derivatives could be used in future related and unrelated research studies including:

- Injecting or transplanting the stem cells or their derivatives into animals for research purposes. Your samples may be used in research that involves genetic manipulation but they will not be used to clone or to otherwise create an entire human being.
- Testing for genetic and DNA composition. Genes may be analyzed and/or manipulated to study normal function or development, and some of the DNA in the stem cells or their derivatives may be altered.
- Other uses involving research or development of commercial products for the diagnosis, prevention, or treatment of various diseases.
- Samples (blood cells, the iPS cells, or their derivatives) obtained from you in this study may be used in the development of one or more diagnostic or therapeutic products which could be patented and licensed by those involved in the research or development of such products. There are no plans to provide financial compensation to you should this occur.

How will I learn the results of this study?

The main way results of research from this study are reported is in scientific publications and presentations at scientific meetings. Summary findings are also sometimes described in our newsletters and on our study website.

We will also report some routine research test measurements to you and/or your health care provider at the time of the exam or after your visit. These may include, for example, blood pressure and cholesterol.

In some cases, if we determine it to be appropriate, we may report to you and/or your health care provider research findings as they relate to you, if you give your permission. This information, if it is reported, might be reported long after your visit for a number of reasons. As an example, it might take years of work to analyze information and arrive at research findings, possibly using newly developed scientific methods.
Our genetic research might generate findings that could be relevant to you and possibly your family members, such as information about a particular genetic variant that might put you at risk of a serious health condition. At this time, we believe that most of the genetic research findings do not have medical importance to individuals, but the field of genetics is changing rapidly.

We currently do not have specific plans to contact you or your health care provider about genetic or non-genetic research findings other than some routine research test measurements. In general, we cannot commit to providing any other research findings to you. In determining whether we share additional research information with you, we will take into account a number of considerations on a case-by-case basis. These might include whether the findings were based on tests that are clinically acceptable, accurate and reliable, whether the findings reveal a significant risk of a serious health condition, whether there is, at the relevant time, a recognized treatment or prevention intervention or other available actions that have the potential to change the clinical course of the health condition, whether reporting or not reporting the results is likely to increase the risk of harm to you, and other relevant factors that we might not be able to predict at this time. In the cases when genetic research findings are reported to you, a study investigator and genetic counselor will contact you to confirm your continued interest in hearing about genetic research results. If you confirm your interest, the study staff will inform you of the research results and recommend next steps such as obtaining confirmatory clinical testing and speaking with your personal healthcare provider.

Research test measurements and findings are not the same as clinical test results. As such, our research examination is not necessarily performed by individuals with clinical training and qualifications, and many parts of the examination do not meet the standards for certified clinical testing. For these reasons, our research tests should not be relied on to make any diagnosis, treatment, or health planning decisions. We do not provide health care or give medical advice or genetic testing or provide counseling. If you or your health care provider decides that follow-up tests or treatments are necessary, then you (or a third party such as a health insurance carrier or Medicare) will be responsible for the cost.

How are my samples and information shared with other researchers?

Samples and information will be kept indefinitely. If you agree, your data and donated blood, blood cells, resulting iPS cells or their derivatives, urine, and any other specimens may be shared with other researchers. These include other academic, non-profit, and for-profit entities, including but not limited to hospitals, universities, cell/tissue storage banks and repositories, databanks and data repositories and businesses, whether for related or unrelated research studies. The cell/tissue storage banks and repositories, databanks and data repositories, include but are not limited to, NIH repositories dbGaP and BioLINCC. Internal and external researchers may request data and materials for research. The repositories have standard operating procedures to protect your confidentiality. Your data and samples will not be labeled with your name or other direct personal identifiers, only a code.

Coded audio recording information will be analyzed by qualifying collaborators inside and outside of BUMC. Your name and other direct personal identifiers will not be shared with these entities.

You have the right to refuse to allow your data and samples to be used or shared for further research. Please check the appropriate box in the selection below.

If you give your permission to allow your data and biological samples to be used or shared for further research, you may withdraw your permission at any time by contacting the FHS investigators. However, if your data or samples have already been released to other researchers, we will not be able to instruct the other researchers to stop using them, to destroy them or products made from them. Your data and samples will not include your name or other direct identifiers.

What risks can I expect?

General risks and individual risks related to new activities are discussed above.

Participating in genetic research could have a negative impact on you, your family, and your loved ones. The genetic studies might result in research findings that relate to your risk of a serious health condition or other genetic information that we might consider to be appropriate to report to you and your health care provider, if you wish us to report them (see below). This could present you with some difficult decisions regarding the available information and the disease risks you and your family members might face. Knowledge of genetic research findings can provoke anxiety and influence decisions regarding marriage, family planning, and other matters. There is a potential risk that your genetic information could be used to your disadvantage. For example, if genetic research findings suggest a serious health problem, that could be used to make it harder for you to get or keep a job or insurance. Both Massachusetts state laws and federal laws, particularly the Genetic Information Nondiscrimination Act (GINA), generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. These laws will generally protect you in the following ways:

1. Health insurance companies and group health plans may not request your genetic information that we get from this research.
2. Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
3. Massachusetts employers with 6 or more employees (or 15 or more employees in other states, under GINA) may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that neither Massachusetts law nor GINA protects you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Thus, life insurance, disability insurance, and long-term care insurance companies may legally ask whether you have had genetic testing and deny coverage for refusal to answer this question.

How is my information protected?

We will store your information in ways we think are secure. We label your samples and information with a code, and we keep the key to the code in a password protected database.

Only approved staff is given the password. We use other safeguards at our facilities and for our information technology and systems to protect the privacy and security of your information.

We do not sell, rent, or lease your contact information.

If information from this study is published or presented at scientific meetings, and when your samples and information are shared with other researchers and deposited in data and specimen banks and repositories, your name and other direct personal identifiers will not be used.

However, we cannot guarantee total privacy. We may provide access to your information in order to do the study and to make sure we do the study according to certain standards set by ethics, law, and quality groups. Information may be made available to researchers that are part of this study, the Institutional Review Board that oversees this research, research and non-research staff and organizations who need the information to do their jobs for the conduct and oversight of the study, people or groups that we hire to do work for us (such as data or biosample storage companies, insurers, and lawyers), and Federal and state agencies as required by law or if they are involved in the research or its oversight. In most cases, any information that is given out to others is identified by code and not with your name or other direct personal identifiers. Once information is given to outside parties, we cannot promise that it will be kept private. Please be aware that your personal information may be given out if required by law (e.g., to prevent possible injury to yourself or others).

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. All studies funded by the National Institutes of Health that involve identifiable information or biological samples are covered by a CoC. The CoC provides how we can share research information or biological samples. Because we have a CoC, we cannot give out research information or biological samples that may identify you to anyone that is not involved in the research except as we describe below. Even if someone tries to get your information or biological samples in connection with a legal proceeding, we cannot give it to them. The CoC does not prevent you from sharing your own research information.

If you agree to be in the study and sign this form, we will share information and biological samples that may show your identity with the following groups of people:

- People who do the research or help oversee the research, including safety monitoring.
- People from Federal and state agencies who audit or review the research, as required by law. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health.
- Investigators who will get your data and your biological samples as we described in the section "*What will happen in this research study?"* These people are expected to protect your information and biological samples in the same way we protect it.
- Any people who you give us separate permission to share your information.

You should know that we are required to report information about child abuse or neglect; elder abuse; specific reportable diseases; or harm to others.

We will share research data where we have removed anything that we think would show your identity. There still may be a small chance that someone could figure out that the information is about you. Such sharing includes:

- Publishing results in a medical book or journal.

- Adding results to a Federal government database
- Using research data in future studies, done by us or by other scientists.
- Using biological samples in future studies, done by us or by other scientists.

Samples that are collected from you in this study will be analyzed to find out information about your genetic makeup. Your genetics and health information, without your name or other data that could easily identify you, will be put in a database run by the National Institutes of Health (NIH). This may include your whole genome information. Other researchers can ask the NIH to get your information from the database. You should know that it is possible that your genetics information might be used to identify you or your family, though we believe it is not too likely that this will happen. Once your information is given to the NIH database, you can ask to have NIH stop sharing it, but NIH cannot take back information that was already shared.

Patenting Discoveries

Research from this study may, one day, result in new tests to diagnose or predict diseases. It may also lead to the development of new ways to prevent or treat diseases. As is true of all federally-funded research, researchers and their employers are permitted by Federal law to patent discoveries from which they may gain financially. You and your heirs will not benefit financially.

What are the possible benefits from being in this research study?

While you will not receive any direct benefit as a result of your participation in this study; we hope that this study will help us better understand what causes heart disease and other diseases and conditions and how to better prevent and treat them.

What are the costs of taking part in the study?

Costs that you may incur on the day of your participation include, but are not limited to, loss of work and transportation costs (gas, tolls, etc.).

You will not be paid for your participation in this study.

No special arrangement will be made by the Framingham Heart Study for compensation or payment solely because of your participation in this study. If you think you have been injured by being in this study, please let the investigators know right away. Boston University and the sponsors do not offer a program to provide compensation for the cost of care for research related injury or other expenses such as lost wages, disability, pain, or discomfort. You will be sent a bill for the medical care you receive for research injury if your medical insurance does not pay for your medical care. This does not waive any of your legal rights.

How long will I be in the study?

FHS is a long-term study.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

The investigator may decide to discontinue your participation without your permission because he/she may decide that staying in the study will be bad for you, or the sponsor may stop the study.

Please read the following statements and check the appropriate box below:

1) I agree to participate in the FHS examination, including the collection of data, blood, urine samples, and various research tests and measurements. I agree to the use of all data, samples, and research materials for studies of the factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other diseases and health conditions.

   | _| YES | _| NO (*For Internal Use - Office Code 0*)

2) I agree to allow my data, blood, DNA and other genetic material, iPS cells and their derivatives, urine samples, and any other specimens to be used in genetic research, of factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other diseases and health conditions.

   | _| YES | _| NO (*For Internal Use - Office Code* 3)

3) I agree to allow researchers from commercial companies to have access to my data, blood, DNA and other genetic material, iPS cells and their derivatives, urine samples, and any other specimens for research. I understand that my data and specimens will be shared without my name or direct personal identifiers.

   | _| YES | _| NO (*For Internal Use - Office Code 4*)

4) I agree to allow the FHS to release the findings of non-genetic research tests and examinations to me and/or my physician, clinic, hospital, or other health care provider.

   | _| YES | _| NO (*For Internal Use - Office Code 30*)

5) I agree to allow the FHS to provide me, and with my permission, my physician, clinic, hospital, or other health care provider information relating to genetic research findings as they may relate to me.

   | _| YES | _| NO (*For Internal Use - Office Code 31*)

Subject: _____
Printed name of subject

By signing this consent form, you are indicating that

- you have read this form (or it has been read to you)
- your questions have been answered to your satisfaction
- you voluntarily agree to participate in this research study
- you permit the use and sharing of information that may identify you as described, including your health information.

To be completed by subject if personally signing

_____ _____
Signature of subject Date

To be completed by LAR if subject does not personally sign
I am providing consent on behalf of the subject.

_____ _____
Printed name of Legally Authorized Representative (LAR) Relationship to Subject

_____ _____
Signature of Legally Authorized Representative Date

Researcher: _____
Printed name of person conducting consent discussion

To be completed by researcher if subject personally signs
I have personally explained the research to the above-named subject and answered all questions. I believe that the subject understands what is involved in the study and freely agrees to participate.

_____ _____
Signature of person conducting consent discussion Date

To be completed by researcher if subject does not personally sign
I have personally explained the research to the above-named subject's Legally Authorized Representative and answered all questions. I believe that the Legally Authorized Representative understands what is involved in the study and freely agrees to have the subject participate.

I consider that the above-named subject (check one):
☐ is capable of understanding what is involved in the study and freely agrees to participate.
☐ is not capable of understanding what is involved in the study.

_____ _____
Signature of person conducting consent discussion Date

Framingham Heart Study
Offspring Exam 10, Omni 1 Exam 5
Brain Health Study

RESEARCH CONSENT FORM ADDENDUM

Basic Information

Title of Project: Multidimensional Assessment of Brain Health as a Marker of Dementia Risk and Resilience

IRB Number: H-40757

Sponsor: National Institute on Aging (NIA), National Institutes of Health (NIH)

Principal Investigator: Sudha Seshadri, MD [redacted]

Please take time to review this information carefully. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Voluntary Participation - You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are entitled.

The PI of the Brian Health Study is Dr. Sudha Seshadri who is Professor of Neurology at the University of Texas Health Sciences Center, San Antonio, TX and also an adjunct Professor of Neurology at Boston University School of Medicine. [redacted] is also the PI of the overall Framingham Heart Study.

Study Phone [redacted]

Overview of the Brain Health Study
We are interested in finding a way to define brain health beyond the evaluation of cognitive testing. We will ask you to participate in a number of sensory motor tests that capture your brain health, including testing your vision, hearing, and motor function. You will have eye testing (without dilatation); hearing testing (using an iPad and headphones); and motor function testing (includes gait speed assessment on an electronic gait mat, during normal walk and while doing a mental task like counting.) As described in the main consent form, we may also report some routine research test measurements to you and/or your health care provider at the time of the exam or after your exam

The Brain Health Study within the Framingham Heart Study Offspring Exam 10, Omni 1 Exam 5 is conducted in collaboration with The University of Texas Health Science Center at San Antonio.

All procedures described below will be performed for research purposes only.
A. Vision Testing:

Optical Coherence Tomography Angiography (OCTA):
This exam will be performed without dilating eye drops. You will be asked to rest your chin and forehead on a support that is attached to the OCT machine. You will be asked to fixate your eyes on a target for a few moments and as a camera scans and takes images of the retina, the back of your eye. It also measures blood flow in the eye and is a completely non-invasive measurement that is approved by the U.S. Food and Drug Administration (FDA) as a rapid method of assessing retinal capillary density

B. **Motor Testing**

In ***Gait Testing***, you will be asked to walk on a gait mat (that appears like a regular rug or mat) that has pressure sensors below it. A computer and software connected to the mat will capture the different aspects of the walk including speed, step length, step width, etc. You will be asked to walk at your usual pace, fast pace and while doing cognitive tasks like counting backwards.

C. Hearing Testing
Using a portable tablet-based system and earphones we will present a **pure tone** to the **ear** measuring the lowest intensity in decibels (dB) at which this **tone** is perceived 50% of the time. This measurement is called **threshold**.

Risks of Participation in this research

Informational risks related to the study
Your data will be assigned a code number. Your name, medical record number, or other information that easily identifies you will not be stored with your samples or data. The key that links your identifying information to the code number will be stored securely in a separate file and will not be shared with researchers that are not part of our study team.
The main risk of allowing us to use your data for research is a potential loss of privacy. This risk is serious but rare because we take many steps to protect your information. We protect your privacy by coding your data and removing personal identifiers. Research results obtained in this study will not be placed in your medical record unless we contact you with a finding of high medical importance. We do not think that there will be further risks to your privacy by sharing your data with other researchers; however, we cannot predict how this data will be used in the future.

Risks of Study Procedures
There is also minimal risk of falling during the gait testing, but we will take the same precautions described above to prevent falls by walking behind and to the side and assisting if required.

For more information about risks and side effects, ask one of the researchers or study staff. We will tell you about any significant new findings which develop during the course of this research which may relate to your willingness to continue taking part.

What if a research-related injury occurs?
The researchers have taken steps to minimize the known or expected risks and we expect no injuries from these studies. However, you may still experience problems or side effects, even though the researchers are careful to avoid them. in the event of a research-related injury or if you experience an adverse reaction, please immediately contact study staff. See the section "Contact Information" for phone numbers and additional information. You may also need to tell your regular doctors.

If you are injured or made sick from taking part in this research study, medical care will be provided. This care may be billed to you or your insurance. Depending on the circumstances, this care may be provided at no cost to you. We do not offer a program to provide compensation for the cost of care for research related injury. The study staff can provide you with more information.

If you sign this form, you do not give up your right to seek additional compensation if you are harmed as a result of being in this study

Information about how this study will use your Protected Health Information (PHI)
Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of monitoring research may want to see study records which identify you as a subject in this study.

Research policies require that private information about you be protected and this is especially true for your health information. However, the law sometimes allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study.

What is Protected Health Information (PHI)?
Protected Health Information is information about a person's health that includes information that would make it possible to figure out who the person is. According to the law, you have the right to decide who can see your protected health information. If you choose to take part in this research study, you will be giving your permission to the investigators and the research study staff (individuals carrying out the study) to see and use your health information for the study. In carrying out this research, the health information we will see and use about you will include:

- your medical history and blood work,
- results of eye, ear and gait assessment tests,
- information from interviews or from questionnaires,
- demographic information like your age, sex

We will get this information from the data collected today and over the years at the Framingham Heart Study

How will your PHI be protected?
In an effort to protect your privacy, the study staff will use code numbers instead of your name, to identify your health information. Initials and numbers will be used on any photocopies of your

study records, and other study materials containing health information that are sent outside the institutions listed above for review or testing. If the results of this study are reported in medical journals or at meetings, you will not be identified.

Parts of your PHI may be photocopied and sent to a central location or it may be transmitted electronically, such as by e-mail, fax, or other secure means of transmission. The groups receiving your health information may not be obligated to keep it private. They may pass information on to other groups or individuals not named here.

How will your PHI be shared with other Researchers?
Because it is research, we will be unable keep your PHI completely confidential. We may share your health information with people and groups involved in conducting and overseeing this research study including:

- the following collaborators at other institutions that are involved with the study: The University of Texas Health Science Center at San Antonio, Boston University School of Medicine, Massachusetts Eye and Ear Infirmary and University of Southern California
- the members of the local research team;
- the Institutional Review Board and the Compliance Office of the University of Texas Health Science Center at San Antonio, and other groups that oversee how research studies are carried out; and
- the Research offices at the University of Texas Health Science Center at San Antonio

If you decide to participate in this study, you will be giving your permission for the groups named above, to collect, use and share your health information for research purposes. If you choose not to let these groups collect, use and share your health information as explained above, you will not be able to participate in this research study.

Do you have to allow the use of your health information?
You do not have to allow (authorize) the researchers and other groups to see and share your health information. If you choose not to let the researchers and other groups use your health information, there will be no penalties, but you will not be allowed to participate in the Brain Health Study portion part of the Framingham Heart Study Examination.

After you enroll in this study, you may ask the researchers to stop using your health information at any time. However, you must provide this in writing and send your letter to ***Vasan Ramachandran, Principal Investigator, Framingham Heart Study, 73 Mt Wayte Ave, Suite 2, Framingham, MA 01702.*** If you tell the researchers to stop using your health information, your participation in this part of the Framingham Heart study will end and the study staff will stop collecting new health information from you and about you for this study. However, the study staff will continue to use the health information collected up to the time they receive your letter asking them to stop.

Can you ask to see the PHI that is collected about you for this study?
The federal rules say that you can see the health information that we collect about you and use in this study. Contact the study staff if you have a need to review your PHI collected for this study. If you ask for research information that is not in your medical record, we might not

provide it to you, but we will explain why not. You may use the contact information on the first page of this form to find out how to get your health information.

How long will your PHI be used?
By signing this form, you agree to let us use and disclose your health information for purposes of the study until the end of this study; at this time we do not have any specific end date and will continue using your data until it is no longer of scientific value.

Contact Information
If you have questions now, feel free to ask us. If you have additional questions later or you wish to report a problem or complaint which may be related to this study please contact:

[redacted]

Research Consent & Authorization Signature Section

If you agree to participate in this research and agree to the use of your protected health information in this research sign this section. You will be given a signed copy of this form to keep. You do not waive any of your legal rights by signing this form.

SIGN THIS FORM ONLY IF THE STATEMENTS LISTED BELOW ARE TRUE

- You have read the above information.
- Your questions have been answered to your satisfaction.

Adult Signature Section

- You have voluntarily decided to take part in this research study.
- You authorize the collection, use and sharing of your protected health information as described in this form.

Printed Name of Subject	Signature of Subject	Date

Surrogate Signature Section

- You are voluntarily giving your consent for another person to participate in this study because you believe this person would want to take part if able to make the decision and you believe it is in this person's best interest.
- You are authorizing the collection, use and sharing of another person's protected health information as described in this form.

Printed Name of Subject	Signature of **Subject**, indicating Assent *(If incapable of signing, person obtaining consent should initial here)*	Date
Printed Name of Legally Authorized Representative (LAR)	Signature of Legally Authorized Representative (LAR)	Date

Researcher

Printed Name of Person Obtaining Consent and Authorization	Signature of Person Obtaining Consent & Authorization	Date

BMC and BU Medical Campus IRB
IRB NUMBER: H-32132
IRB APPROVAL DATE: 07/21/2021

Framingham Heart Study
Offspring Exam 10, Omni 1 Exam 5
Bone Study Informed Consent Form ADDENDUM

Basic Information

Title of Project: Framingham Heart Study

IRB Number: H-32132

Sponsor: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)

Principal Investigator: Vasan S. Ramachandran, MD

[redacted]

Study Phone Number: [redacted]

PI Phone Number: [redacted]

Overview of the Bone Study at the Framingham Heart Examination

We are interested in learning about how the skeleton changes with aging. We will ask you to participate in two bone scans to examine the bone structure in your lower leg and lower arm. The scan is a non-invasive and painless test, and provides a detailed image of the "micro-architecture" inside the bone. Each scan takes about two minutes and requires that you keep as still as possible.

The research examination that will be conducted as part of this study is not clinical care. The tests are for research purposes only. We do not provide medical services. This research examination does not take the place of medical care by your own health care provider.

About your consent

Please read this research consent form carefully. It tells you important information about the research study. Taking part in a research study is voluntary. The decision whether or not to take part in all or any part of the research exam is entirely up to you. If you choose to take part, you can decide to stop at any time. Your decision will be honored and respected. There will be no penalty to you if you decide to stop or not to take part.

If I have questions or concerns about this research study, whom can I call?

If you have any questions about the research or about this form, please ask us. You can call us with your questions or concerns. You can ask questions as often as you want.

You can call a study staff member directly at [redacted]

The Framingham Heart Study is led by investigators from Boston University and the National, Heart, Lung, and Blood Institute at the National Institutes of Health. [redacted]

[redacted] You will be talking to someone at the Boston Medical Center and Boston University Medical Campus IRB. The IRB is a group that helps monitor research. You should call or email the IRB if you want to find out about your rights as a research subject. You should also call or email if you want to talk to someone who is not part of the study about your questions, concerns, or problems.

Overall Examination Risks and Discomforts
Bone scans involve the use of x-rays, a form of energy also called radiation. The radiation dose for the two scans together will be less than 10 μSv, which is equivalent to 2-3 days of background radiation that individuals experience in the U.S. Since the amount of radiation from the bone scans is so small, there are no known long-term effects of this radiation on your health. However due to potential risk to a fetus, pregnant women, as determined by self-report or by a positive pregnancy test, will be excluded from this test.

We do not expect any risk of injury as a result of your participation in the study. However, first aid will be available.

Unknown Risks: There may also be some risks that we are unable to determine at this time.

How is my information protected?

We will store your information in ways we think are secure. We label your samples and information with a code, and we keep the key to the code in a password protected database. Only approved staff is given the password. We use other safeguards at our facilities and for our information technology and systems to protect the privacy and security of your information.

We do not sell, rent, or lease your contact information.

If information from this study is published or presented at scientific meetings, and when your samples and information are shared with other researchers and deposited in data and specimen banks and repositories, your name and other direct personal identifiers will not be used.

However, we cannot guarantee total privacy. We may provide access to your information in order to do the study and to make sure we do the study according to certain standards set by ethics, law, and quality groups. Information may be made available to researchers that are part of this study, the Institutional Review Board that oversees this research, research and non-research staff and organizations who need the information to do their jobs for the conduct and oversight of the study, people or groups that we hire to do work for us (such as data or biosample storage companies, insurers, and lawyers), and Federal and state agencies as required by law or if they are involved in the research or its oversight. In most cases, any information that is given out to others is identified by code and not with your name or other direct personal identifiers. Once information is given to outside parties, we cannot promise that it

will be kept private. Please be aware that your personal information may be given out if required by law (e.g., to prevent possible injury to yourself or others).

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. All studies funded by the National Institutes of Health that involve identifiable information or biological samples are covered by a CoC. The CoC provides how we can share research information or biological samples. Because we have a CoC, we cannot give out research information or biological samples that may identify you to anyone that is not involved in the research except as we describe below. Even if someone tries to get your information or biological samples in connection with a legal proceeding, we cannot give it to them. The CoC does not prevent you from sharing your own research information.

If you agree to be in the study and sign this form, we will share information and biological samples that may show your identity with the following groups of people:

- People who do the research or help oversee the research, including safety monitoring.
- People from Federal and state agencies who audit or review the research, as required by law. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health.
- Investigators who will get your data and your biological samples as we described in the section "*What will happen in this research study?"* These people are expected to protect your information and biological samples in the same way we protect it.
- Any people who you give us separate permission to share your information.

You should know that we are required to report information about child abuse or neglect; elder abuse; specific reportable diseases; or harm to others.

We will share research data where we have removed anything that we think would show your identity. There still may be a small chance that someone could figure out that the information is about you. Such sharing includes:

- Publishing results in a medical book or journal.
- Adding results to a Federal government database
- Using research data in future studies, done by us or by other scientists.
- Using biological samples in future studies, done by us or by other scientists.

Samples that are collected from you in this study will be analyzed to find out information about your genetic makeup. Your genetics and health information, without your name or other data that could easily identify you, will be put in a database run by the National Institutes of Health (NIH). This may include your whole genome information. Other researchers can ask the NIH to get your information from the database. You should know that it is possible that your genetics information might be used to identify you or your family, though we believe it is not too likely that this will happen. Once your information is given to the NIH database, you can ask to have NIH stop sharing it, but NIH cannot take back information that was already shared.

Patenting Discoveries

Research from this study may, one day, result in new tests to diagnose or predict diseases. It may also lead to the development of new ways to prevent or treat diseases. As is true of all federally-funded research, researchers and their employers are permitted by Federal law to

patent discoveries from which they may gain financially. You and your heirs will not benefit financially.

What are the possible benefits from being in this research study?

While you will not receive any direct benefit as a result of your participation in this study; we hope that this study will help us better understand what causes heart disease and other diseases and conditions and how to better prevent and treat them.

What are the costs of taking part in the study?

Costs that you may incur on the day of your participation include, but are not limited to, loss of work and transportation costs (gas, tolls, etc.).

You will not be paid for your participation in this study.

No special arrangement will be made by the Framingham Heart Study for compensation or payment solely because of your participation in this study. If you think you have been injured by being in this study, please let the investigators know right away. Boston University and the sponsors do not offer a program to provide compensation for the cost of care for research related injury or other expenses such as lost wages, disability, pain, or discomfort. You will be sent a bill for the medical care you receive for research injury if your medical insurance does not pay for your medical care. This does not waive any of your legal rights.

How long will I be in the study?

FHS is a long-term study.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

The investigator may decide to discontinue your participation without your permission because he/she may decide that staying in the study will be bad for you, or the sponsor may stop the study.

Subject: _____
Printed name of subject

By signing this consent form, you are indicating that

- you have read this form (or it has been read to you)
- your questions have been answered to your satisfaction
- you voluntarily agree to participate in this research study
- you permit the use and sharing of information that may identify you as described, including your health information.

To be completed by subject if personally signing

_____ _____
Signature of subject Date

To be completed by LAR if subject does not personally sign
I am providing consent on behalf of the subject.

_____ _____
Printed name of Legally Authorized Representative (LAR) Relationship to Subject

_____ _____
Signature of Legally Authorized Representative Date

Researcher: _____
Printed name of person conducting consent discussion

To be completed by researcher if subject personally signs
I have personally explained the research to the above-named subject and answered all questions. I believe that the subject understands what is involved in the study and freely agrees to participate.

_____ _____
Signature of person conducting consent discussion Date

To be completed by researcher if subject does not personally sign
I have personally explained the research to the above-named subject's Legally Authorized Representative and answered all questions. I believe that the Legally Authorized Representative understands what is involved in the study and freely agrees to have the subject participate.

I consider that the above-named subject (check one):
☐ is capable of understanding what is involved in the study and freely agrees to participate.
☐ is not capable of understanding what is involved in the study.

_____ _____
Signature of person conducting consent discussion Date

Estudio del Corazon de Framingham,
examen 10 de Offspring, examen 5 de Omni 1

FORMULARIO DE CONSENTIMIENTO PARA LA INVESTIGACIÓN

Bienvenido nuevamente al Estudio del Corazón de Framingham

Juntos estamos ayudando a combatir las enfermedades cardíacas y otras enfermedades y problemas de salud importantes mediante la investigación.

Información básica

Título del proyecto: Estudio del Corazón de Framingham

Número de la IRB: H-32132

Patrocinador: Instituto Nacional del Corazón, los Pulmones y la Sangre (National Heart, Lung, and Blood Institute, NHLBI), Institutos Nacionales de Salud (National Institutes of Health, NIH)

Investigador principal: Vasan S. Ramachandran, MD
[redacted]

Número de teléfono del estudio: [redacted]

[redacted]

¿Por qué se está haciendo este estudio de investigación?

El Estudio del Corazón de Framingham es un estudio de investigación a largo plazo. Su propósito es el siguiente:

(1) ayudar a comprender cómo se desarrollan las enfermedades del corazón y los vasos sanguíneos, las enfermedades de los pulmones y la sangre, los accidentes cerebrovasculares, la pérdida de memoria, el cáncer y otras enfermedades y afecciones de salud importantes;

y

(2) examinar el ADN y su relación con los riesgos de desarrollar estas enfermedades y otras afecciones de salud.

El examen que se llevará a cabo como parte de este estudio de investigación no es igual a la atención médica en una clínica. Las pruebas son solo con fines de investigación. No ofrecemos servicios médicos. Este examen no reemplaza su control con su proveedor de atención médica.

Acerca de su consentimiento

Lea atentamente este formulario de consentimiento de investigación. Le brinda información importante sobre el estudio. La participación en un estudio de investigación es voluntaria. La decisión de participar o no, ya sea en parte o en la totalidad del examen, depende completamente de usted. Si usted elige participar, puede decidir dejar de hacerlo en cualquier momento. Su decisión será aceptada y respetada. No habrá ninguna sanción si decide no participar o dejar de participar.

¿A quién puedo llamar si tengo preguntas o dudas acerca de este estudio de investigación?

Si tiene alguna pregunta acerca de este estudio o de este formulario, consúltenos. Puede llamarnos por preguntas o dudas las veces que desee.

Puede llamar directamente a un miembro del personal del estudio al (508) 872-6562 o al (800) 854-7582, o puede enviar un correo electrónico a FHS@bu.edu.

El Estudiodel Corazón de Framingham es realizado por los investigadores de la Universidad de Boston, el Instituto Nacional Cardíaco, Pulmonar y Sanguíneo, y el Instituto Nacional de la Salud. [redacted] Se comunicará con una persona del Centro Médico de Boston y de la Junta de Revisión Institucional (*Institutional Review Board*, IRB) del Campus Médico de la Universidad de Boston (Boston University Medical Campus, BUMC). La IRB es un grupo que ayuda a supervisar las investigaciones. Si desea conocer sus derechos como sujeto de una investigación, debe llamar o enviar un correo electrónico a la IRB. Comuníquese también con esta agencia si desea hablar sobre sus preguntas, inquietudes o problemas con una persona ajena a este estudio.

¿Qué sucederá en este estudio de investigación?

Usted deberá ayunar durante 10 horas antes de llegar a su cita debido a la muestra de sangre que tomaremos. Si toma algún medicamento en la mañana, hágalo como siempre. Puede continuar bebiendo agua durante el ayuno.

Su examen se llevará a cabo en el Centro de Investigación del Estudio del Corazón de Framingham (*Framingham Heart Study*, FHS) en 73 Mount Wayte Avenue, Framingham, MA, por teléfono o videoconferencia (también llamada *teleconsulta*), o en su casa u otra residencia. El examen completo en el lugar tomará alrededor de 4 a 5 horas. También se puede dividir en varias partes: 2 horas por teleconsulta y 2,5 horas por consulta en persona en el Centro de Investigación. Los componentes del examen que puedan completarse a la distancia se incluirán durante la teleconsulta y los que requieran una evaluación en persona se llevarán a cabo en el Centro de Investigación o en su casa u otra residencia.

Como en los exámenes anteriores:

- Tomaremos una muestra de sangre para pruebas genéticas y de laboratorio, para poder comprender mejor los factores de riesgo de enfermedades del corazón y otras enfermedades bajo estudio (por ejemplo, la cantidad y la función de diferentes tipos de colesterol en la sangre). La cantidad total de sangre extraída será alrededor de 80 ml, que son unas 5,4 cucharadas. La extracción de sangre

se realizará poco después de su llegada.
- Recolectaremos una muestra de orina.
- Mediremos su altura, peso y cintura.
- Mediremos la fuerza de agarre.
- Realizaremos un electrocardiograma (ECG).
- Mediremos su presión arterial.
- Actualizaremos su historia clínica.
- Haremos una prueba de la función vascular cardíaca (tonometría) que examina la función cardíaca mediante una ecografía (ecocardiograma) y evalúa la rigidez de los vasos sanguíneos (arterias) mediante el registro de la presión arterial y las formas de onda del flujo.
- Le pediremos que firme un formulario de consentimiento para que nos dé permiso de obtener copias de los expedientes médicos, incluidos los de Medicare. Este formulario será válido hasta que usted lo cancele.
- Lo contactaremos más adelante por correo, correo electrónico o por teléfono (llamada o mensaje de texto) para obtener información adicional o para invitarlo a participar en otros estudios relacionados con el FHS. También puede ser invitado a participar de nuevo a otro de nuestros exámenes.

Encuestas
También le pediremos que llene unos cuestionarios sobre, por ejemplo, la función física, dieta, ejercicio, memoria y estado de ánimo y sus hábitos de estilo de vida, incluyendo si fuma o consume alcohol. Algunos de los cuestionarios ya los ha hecho, otros serán nuevos para usted.

Algunas de sus respuestas se grabarán mediante una grabadora audio-digital. Las grabaciones serán analizadas junto con otra información del estudio. También usaremos las grabaciones para asegurarnos de que sus respuestas estén documentadas correctamente.

Hay algunas nuevas actividades de investigación.

1. Fibroscan: Estamos interesados en mejorar nuestra comprensión sobre los factores que pueden ayudar a predecir el desarrollo de grasa hepática y fibrosis hepática (cicatrización). Para este estudio, se le realizará una prueba llamada Fibroscan. El fibroscan mide la presencia de grasa o cicatrices en el hígado. Se genera un pulso sin dolor en la piel que viaja al hígado y mide su dureza.

   ¿Qué riesgos puedo esperar? Puede haber pequeñas molestias por la aplicación del gel y la presión sobre la piel con la punta del aparato fibroscan. Sin embargo, no hay riesgos conocidos asociados con el fibroscan.

   Hay algunas condiciones que pueden interferir con la capacidad del dispositivo para obtener medidas válidas. Estas incluyen las siguientes: estar embarazada, tener líquido en la cavidad abdominal (ascitis) y tener implantes médicos, como un marcapasos. Le pediremos que nos confirme si tiene alguna de estas condiciones para no realizar el fibroscan.

2. Estudio de evaluación del dolor: Estamos interesados en conocer sobre el dolor que las personas pueden experimentar en su vida diaria y comprender mejor por qué algunas personas sienten dolor y otras no o por qué unas personas sienten más dolor que otras, o por qué algunas personas sienten dolor en más partes del cuerpo que otras. Le haremos algunas preguntas sobre el dolor y evaluaremos su sensibilidad a la presión sobre la piel. Para evaluar su sensibilidad a la presión, se presionará un pequeño

dispositivo contra un músculo del hombro y se medirá cuánta presión se aplica antes de que sienta alguna molestia.

¿Qué riesgos puedo esperar? Aunque es poco común, existe la posibilidad de que se produzca irritación de la piel y enrojecimiento o hematomas durante la prueba. Es posible que aparezcan moretones o molestias por la aplicación del medidor de presión durante la prueba del umbral de dolor por presión o por el inflado del manguito del tensiómetro.

3. Estudio de salud del cerebro: Estamos interesados en encontrar otra forma distinta a la evaluación de las pruebas cognitivas para definir la salud del cerebro. Le pediremos que participe en una serie de pruebas motoras que capturarán la salud de su cerebro, que incluyen pruebas de la visión, audición y función motora. Se le realizará una prueba de ojos (sin dilatación); pruebas de audición (usando un iPad y auriculares); y pruebas de la función física (incluye la evaluación de la velocidad de la marcha en una alfombra electrónica, la evaluación durante la caminata normal y mientras se realiza una tarea mental, como contar, y la evaluación cronometrada de ponerse de pie desde una silla).

   ¿Qué riesgo puedo esperar? No existe ningún riesgo en las pruebas de ojos y audición. La prueba de la marcha tiene un riesgo mínimo de caída. Se tomarán todas las precauciones para evitar que esto ocurra. Un miembro del personal del estudio estará cerca de usted para evitar que se caiga y lo ayudará en caso de ser necesario.

4. Estudio electrónico del FHS (eFHS): Si vive en los Estados Unidos, tiene correo electrónico y acceso diario a Internet o un teléfono inteligente, lo invitamos a participar en el estudio eFHS. Para participar es necesario que ingrese a una plataforma web, descargue las aplicaciones y use dispositivos inalámbricos. Las aplicaciones requieren completar encuestas sobre salud y estilo de vida. Los dispositivos electrónicos miden la frecuencia cardíaca, presión arterial, peso y actividad física.

   ¿Qué riesgos puedo esperar? No existen riesgos conocidos por participar en este estudio.

5. Estudio del hueso: Estamos interesados en conocer cómo cambia el esqueleto con el envejecimiento. Le pediremos que participe en dos pruebas de densidad ósea para examinar la estructura ósea de la parte inferior de la pierna y el antebrazo. Es una prueba no invasiva e indolora y proporciona una imagen detallada de la "microarquitectura" del interior del hueso. Cada una dura aproximadamente dos minutos y requiere que se mantenga lo más quieto posible.

   ¿Qué riesgos puedo esperar? Las pruebas de densidad ósea implican el uso de rayos x, que son una forma de radiación. La dosis de radiación para los dos escaneos juntos será inferior a 10 µSv. Esto equivale a 2 o 3 días de radiación de fondo que experimentan las personas en los Estados Unidos. Debido a que la cantidad de radiación de las pruebas de densidad ósea es muy pequeña, no se conocen efectos a largo plazo en su salud por esta radiación.

Algunos de los componentes del estudio descritos en esta sección "¿Qué sucederá en este estudio de investigación?" no se puede administrar durante la teleconsulta, debido a la necesidad de realizar algunas mediciones en persona. Además, algunos de los exámenes del estudio no se pueden realizar fuera del Centro de Investigación, ni en su casa ni en un centro de atención, debido al tamaño del equipo necesario que imposibilita su traslado. Por ejemplo,

el fibroscan, la tonometría y la tomografía computarizada (TC).

Riesgos y malestares generales del examen
Riesgos generales: Este estudio lleva tiempo y es repetitivo. Otras molestias incluyen dolores de cabeza, sentirse con hambre debido al ayuno, tener fatiga y escalofríos durante la visita.

Las pruebas de densidad ósea por TC implican exposición a radiación. Debido a que la cantidad de radiación es muy pequeña, equivale a 2 o 3 días de radiación de fondo y no se conocen efectos a largo plazo en su salud por esta radiación. Sin embargo, debido al riesgo potencial para un feto, las mujeres embarazadas, según lo determinado por un autoinforme o por una prueba de embarazo positiva, serán excluidas de esta prueba.

No esperamos ningún riesgo de lesiones como resultado de su participación en el estudio. Sin embargo, tenemos disponibles primeros auxilios.

Riesgos desconocidos: Existe la posibilidad de otros riesgos que no hemos identificado hasta el momento.

Estudios genéticos
Es posible que ya haya otorgado su consentimiento para la recolección de muestras biológicas para la investigación del ADN o la creación de células madre con pluripotencialidad inducida (*Induced Pluripotent Stem Cells*, células iPS). Planeamos continuar realizando investigaciones genéticas con el ADN de sus muestras biológicas, las cuáles incluyen células sanguíneas, células de los tejidos, etc. El ADN es el material con el que están hechos sus genes. Los genes pasan del padre y la madre al hijo. Todos los seres vivos están compuestos de células. Los genes son la parte de las células que contienen las instrucciones para decirle a nuestro cuerpo cómo crecer y trabajar, y determinar sus características físicas, como cabello y color de ojos.

También, si está de acuerdo, en un laboratorio, procesaremos las células blancas de la sangre de una de sus muestras para convertirlas en células madre. Las células resultantes son conocidas como *células madre con pluripotencialidad inducida* (células iPS) y se utilizan en el laboratorio para que actúen como células de otros órganos; tales como células del hígado, células grasas, células del corazón, células pulmonares, vasculares, intestinales, células nerviosas, diferentes tipos de células sanguíneas y muchos otros tipos de células naturales. Estas células y los productos celulares que pueden obtenerse de ellas, tales como ARN, proteínas y metabolitos, pueden ser estudiados en laboratorios para aprender más sobre las causas de la salud o enfermedad de estos órganos.

Las células serán guardadas indefinidamente en un repositorio de células madre en la Universidad de Boston. Las células también pueden almacenarse en un repositorio central o banco.

Si está de acuerdo, sus tejidos, células o cualquier línea de células iPS o sus derivados podrían ser usados en el futuro para estudios relacionados y no relacionados, como los siguientes:

- Inyección o trasplante de células madre o sus derivados a animales para fines de investigación. Sus muestras podrían ser usadas en estudios que involucran manipulación genética, pero jamás serán usadas para clonar o reproducir a un ser humano completo.
- Pruebas genéticas y composición del ADN. Los genes pueden ser analizados o manipulados para estudiar su función normal y desarrollo. El ADN de

algunas células madre o sus derivados podría ser alterado.

- Otros usos que implican investigación o desarrollo de productos comerciales para el diagnóstico, prevención o tratamiento de diversas enfermedades.
- Las muestras obtenidas de usted en este estudio (células sanguíneas, células iPS o sus derivados) pueden ser utilizadas en el desarrollo de uno o más productos terapéuticos o de diagnóstico que podrían ser patentadas y autorizadas por los investigadores involucrados en la investigación o en el desarrollo de estos productos. No hay planes para proporcionar compensación económica si esto ocurriera.

¿Cómo puedo saber los resultados de este estudio?

La principal manera en que los resultados de este estudio son reportados es a través de publicaciones científicas y con presentaciones en reuniones científicas. En nuestros boletines informativos y en nuestro sitio web del estudio, a veces también describimos los hallazgos resumidos.

También informaremos los resultados de mediciones rutinarias de investigación a usted o a su proveedor de atención médica en el momento del examen o después de su visita. Estos pueden incluir, por ejemplo, la presión arterial y el colesterol.

En algunos casos, si determinamos que es apropiado, podemos informarlo a usted o a su proveedor de atención médica los hallazgos de investigación que se relacionen con usted si nos da su permiso para ello. Esta información, si se da a conocer, podría tomar mucho tiempo después de su visita por una serie de razones: por ejemplo, podría llevar años de trabajo para analizar la información y llegar a resultados de investigación, quizás utilizando métodos científicos que han sido desarrollados solo recientemente.

Nuestra investigación genética podría generar resultados que sean relevantes para usted y, posiblemente, su familia; tales como información sobre una variante genética en particular que lo pudiera poner en riesgo de una afección de salud grave. Por el momento, pensamos que la mayoría de los hallazgos de investigación genética no tienen gran importancia médica para las personas, pero el campo de la genética está cambiando rápidamente.

Actualmente no tenemos planes concretos de contactarlo a usted o a su proveedor de atención médica sobre los resultados de las diferentes investigaciones genéticas o no genéticas, excepto por las mediciones de pruebas rutinarias de la investigación. En general, no nos podemos comprometer a proporcionarle otros resultados del estudio. En cuanto a determinar si compartimos información adicional de la investigación con usted, tendremos en cuenta una serie de consideraciones, según cada caso en particular. Estos pueden incluir si los hallazgos se basaron en pruebas que son clínicamente aceptables, precisas y fiables, si los resultados revelan un riesgo significativo de una afección de salud grave, si existe en el momento pertinente un tratamiento reconocido o la intervención de prevención u otras acciones disponibles que tienen el potencial para cambiar el curso clínico de la condición de salud, si informar o no informar los resultados pudiera aumentar el riesgo de daño a usted, y otros factores relevantes que quizá no seamos capaces de predecir en este momento. En los casos en que se le informen los hallazgos de la investigación genética, un investigador del estudio y un asesor genético se comunicarán con usted para confirmar su interés continuo en conocer los resultados de la investigación genética. Si confirma su interés, el personal del estudio le

informará sobre los resultados de la investigación y le recomendará los siguientes pasos por seguir, como obtener pruebas clínicas de confirmación y hablar con su proveedor de atención médica personal.

Las mediciones y resultados de una investigación científica no equivalen a los resultados de pruebas clínicas. Como tal, nuestro examen de investigación no se realiza necesariamente por personas calificadas con formación clínica, y muchas partes de la examinación no cumplen con las normas requeridas para pruebas clínicas certificadas. Por esta razón, nuestras pruebas de investigación no son confiables para hacer diagnósticos, tratamientos ni decisiones para planes de salud. No brindamos atención médica, no damos consejos médicos, ni pruebas genéticas, ni brindamos asesoramiento. Si usted o su proveedor de atención médica decide hacer pruebas adicionales de seguimiento o los tratamientos necesarios, usted (o un tercero, como una aseguradora médica o Medicare) será responsable por esos costos.

¿Cómo se comparten mis muestras y mi información con otros investigadores?

Las muestras e información serán guardadas indefinidamente. Si está de acuerdo, sus datos y sangre donada, células de sangre, células iPS o sus derivados, orina y otros especímenes pueden ser compartidos con otros investigadores, incluyendo otras entidades académicas con o sin fines de lucro, como hospitales, universidades, bancos de almacenamiento de células/tejidos y repositorios, bases de datos y repositorios de datos y empresas (ya sea con fines relacionados o no con estudios de investigación). Los bancos de almacenamiento de células/tejidos y repositorios, los bancos de datos y los repositorios de datos incluyen, entre otros, los repositorios de los NIH dbGaP y BioLINCC. Los investigadores internos y externos pueden solicitar datos y materiales para la investigación. Los repositorios tienen procedimientos operativos estándar para proteger su confidencialidad. Ninguna muestra o información será etiquetada con su nombre o ningún otro identificador personal. Solo con códigos.

La información de las grabaciones de audio codificadas será analizada por colaboradores calificados dentro y fuera del BUMC. Su nombre y otros identificadores personales directos no se compartirán con estas entidades.

Usted tiene el derecho de negarse a permitir que sus datos y muestras sean usados o compartidos para futuras investigaciones. Marque la casilla correspondiente en la lista de abajo.

Si usted da su permiso para que sus datos y muestras biológicas sean utilizados o compartidos para futuras investigaciones, usted podrá retirar su autorización en cualquier momento comunicándose con los investigadores del FHS. Sin embargo, si sus datos o muestras ya han sido compartidos con otros investigadores, no podremos instruirles para que dejen de usarlos o destruirlos al igual que con los productos hechos de estas muestras. Sus datos y muestras no incluirán su nombre ni otros identificadores directos.

¿Qué riesgos puedo esperar?

Los riesgos generales y los riesgos individuales relacionados con las nuevas actividades se mencionaron anteriormente.

La participación en la investigación genética podría tener un impacto negativo para usted, su familia y sus seres queridos. Los estudios genéticos podrían producir resultados en la investigación que se relacionen con riesgos a una afección de salud grave u otra información

genética que podríamos considerar apropiado informarle a usted y a su proveedor de atención médica, si es que lo desea (véase abajo). Esto podría presentarle algunas decisiones difíciles respecto a la información disponible y correr el riesgo de saber sobre enfermedades que usted y sus miembros familiares pudieran enfrentar. Saber los resultados de una investigación genética podría ocasionar ansiedad e influir en decisiones relacionadas con el matrimonio, la planificación familiar y otros temas. Existe una pequeña posibilidad de riesgo de que su información genética se utilice en su contra. Por ejemplo, si los hallazgos de la investigación genética sugieren un problema de salud grave, eso podría usarse para dificultarle la tarea de conseguir o mantener un trabajo o un seguro. Tanto las leyes estatales de Massachusetts como las leyes federales, en particular, la *Genetic Information Nondiscrimination Act* [Ley de No Discriminación por Información Genética] (GINA), en general, prohíben que las compañías de seguros médicos, los planes médicos grupales y la mayoría de los empleadores lo discriminen en función de su información genética. Estas leyes, generalmente, lo protegerán de las siguientes maneras:

1. Las compañías de seguros médicos y los planes médicos grupales no pueden solicitar la información genética que obtendremos de esta investigación.
2. Las compañías de seguros médicos y los planes médicos grupales no pueden usar su información genética para tomar decisiones sobre su elegibilidad o primas.
3. Los empleadores de Massachusetts con 6 o más empleados (o 15 o más empleados en otros estados, según la GINA) no pueden usar su información genética que obtendremos de esta investigación para tomar la decisión de contratarlo, ascenderlo o despedirlo o para establecer los términos de su empleo.

Tenga en cuenta que ni la ley de Massachusetts ni la GINA lo protegen contra la discriminación genética por parte de compañías que venden seguros de vida, seguros por discapacidad o seguros de atención a largo plazo. Por lo tanto, las compañías de seguros de vida, de discapacidad y de atención a largo plazo pueden preguntarle legalmente si se ha sometido a pruebas genéticas y negarle la cobertura si usted se niega a responderles.

¿Qué tan protegida está mi información?

Almacenaremos su información de formas que consideremos seguras. Etiquetaremos sus muestras e información con un código y mantendremos las claves de los códigos en una base de datos protegida con contraseña. Solo al personal autorizado se le da la contraseña. Usaremos otros medios seguros en nuestras instalaciones y en nuestra tecnología y sistemas de información para proteger su privacidad y su información.

No vendemos, rentamos ni arrendamos su información de contacto.

Su nombre y otros identificadores personales directos no se usarán cuando la información de este estudio es publicada o presentada en reuniones científicas, ni cuando sus muestras o información se comparten con otros investigadores, ni cuando las guardamos en repositorios y bancos de muestras y datos.

Sin embargo, no garantizamos la privacidad total. Nosotros podemos dar acceso a su información para realizar el estudio y para asegurarnos de que hacemos el estudio, según las normas establecidas por la ética, el derecho y los grupos de calidad. La información puede ponerse a disposición de los investigadores que forman parte de este estudio, pero también de la Junta de Revisión Institucional que dirige esta investigación, de empleados y organizaciones que necesitan la información para hacer su trabajo en la realización y supervisión del estudio, personas o grupos que nos contratan para trabajar para nosotros (como empresas de almacenamiento de datos de muestras biológicas, compañías de seguros y abogados) y

organismos federales y estatales, según lo exija la ley o si están implicados en la investigación o supervisión de nuestro estudio. En la mayoría de los casos, cualquier información que se da es identificada con códigos y no con su nombre u otros identificadores personales directos. Una vez que se da información a terceros, no podemos prometer que se mantendrá en privado. Tenga en cuenta que su información personal puede ponerse a disposición si es requerida por la ley (como, por ejemplo, para evitar posibles lesiones a usted o a otros).

Este estudio está cubierto por un certificado de confidencialidad (*Certificate of Confidentiality*, CoC) de los Institutos Nacionales de Salud. Todos los estudios financiados por los Institutos Nacionales de Salud que involucran información identificable o muestras biológicas están cubiertos por un CoC. El CoC determina cómo podemos compartir información de investigación o muestras biológicas. Debido a que tenemos un CoC, no podemos entregar información de investigación o muestras biológicas que puedan identificarlo a ninguna persona que no participe en la investigación, excepto como se describe a continuación. Aunque una persona intentara obtener su información o muestras biológicas para un procedimiento legal, no podemos dársela. El CoC no le impide compartir su propia información de investigación.

Si usted acepta participar en el estudio y firmar este formulario, compartiremos información y muestras biológicas que puedan revelar su identidad con los siguientes grupos de personas:

- Personas que realizan la investigación o ayudan a supervisar la investigación, incluso el control de seguridad.
- Personas de agencias federales y estatales que auditan o revisan la investigación, según lo exige la ley. Dichas agencias pueden incluir las siguientes: el Departamento de Salud y Servicios Sociales de EE. UU., la Administración de Alimentos y Medicamentos, los Institutos Nacionales de Salud y el Departamento de Salud Pública de Massachusetts.
- Los investigadores que obtendrán sus datos y muestras biológicas, según detallamos en la sección "¿Qué sucederá en este estudio de investigación?". Se espera que estas personas protejan su información y muestras biológicas de la misma manera en la que las protegemos nosotros.

- Cualquier persona para la que usted nos haya dado permiso por separado para compartir su información.

Debe saber que estamos obligados a informar sobre abuso o negligencia infantil, maltrato a personas mayores, enfermedades de notificación específicas o daños a otras personas.

Compartiremos los datos de la investigación una vez que hayamos eliminado cualquier cosa que consideremos que podría revelar su identidad. De todas maneras, podría haber una pequeña posibilidad de que alguien pueda averiguar que la información es acerca de usted. Dicha divulgación incluye lo siguiente:

- La publicación de los resultados en revistas o libros médicos.
- La incorporación de los resultados a una base de datos del Gobierno federal.
- El uso de los datos de la investigación en estudios futuros, realizados por nosotros o por otros científicos.
- El uso de las muestras biológicas en estudios futuros, realizados por nosotros o por otros científicos.

Las muestras que se obtengan de usted en este estudio se analizarán para averiguar información sobre su composición genética. Es posible que su información genética y de salud,

sin su nombre ni ningún otro dato que pudiera identificarlo fácilmente, se incluya en una base de datos administrada por los Institutos Nacionales de la Salud (NIH). Esto podría incluir la información completa de su genoma. Otros investigadores pueden solicitarles a los NIH su información de la base de datos. Debe saber que es posible que su información genética podría utilizarse para identificarlos a usted o a su familia, aunque creemos que no es demasiado probable que esto suceda. Una vez que su información se entregue a la base de datos de los NIH, puede solicitar que los NIH dejen de compartirla, pero no podrá recuperar información que ya fue entregada.

Patentes de descubrimientos

Algún día, la investigación de este estudio resultará en nuevas pruebas para diagnosticar o predecir enfermedades. También puede llevar al desarrollo de nuevas formas de prevenir o tratar enfermedades. Como es el caso de todas las investigaciones financiadas por el Gobierno federal, los investigadores y sus empleadores tienen permitido, por la Ley Federal de Patentes de Descubrimientos, beneficiarse financieramente. Ni usted ni sus herederos se beneficiarán financieramente.

¿Cuáles son los posibles beneficios de mi participación en este estudio?

A usted no se le pagará por participar en el estudio ni obtendrá beneficios médicos como resultado de su participación. Sin embargo, esperamos que este estudio nos ayude a comprender mejor qué es lo que causa enfermedades del corazón y otras enfermedades y afecciones, así como las mejores maneras de prevenir y tratar estas enfermedades.

¿Cuáles son los costos por participar en el estudio?

Los costos que pudiera incurrir el día de su participación incluyen, entre otros, costos de transporte (gasolina, peajes, etc.) y el no poder trabajar el tiempo que esté aquí.

Usted no recibirá ningún pago por participar en este estudio.

El Estudio del Corazón de Framingham no hará arreglos especiales de compensación o pago por su participación en este estudio. Si piensa que ha sufrido una lesión por participar en este estudio, comuníqueselo de inmediato al investigador. La Universidad de Boston y los patrocinadores del estudio, no ofrecen un programa de compensación debido al costo por la atención médica que pudiera recibir si sufriera lesiones, discapacidad, dolor, malestar u otros gastos, como pérdida de salario. Si sufriera lesiones aquí y si su seguro médico no cubriera su atención médica, no le compensaremos por el gasto de la atención médica que reciba. Esto no lo hace renunciar a ninguno de sus derechos legales.

¿Cuánto tiempo estaré en el estudio?

El Estudio del Corazón de Framingham es un estudio a largo plazo.

La participación en este estudio depende solo de usted. Puede optar por participar o por no participar. Si ahora decide participar, puede cambiar de opinión y dejar de hacerlo más adelante.

Le haremos saber si encontramos información nueva que pudiera hacerlo cambiar de parecer respecto a su participación en este estudio.

El investigador puede decidir interrumpir su participación sin su autorización debido a que este considera que su continuidad en el estudio podría ser perjudicial para usted o el patrocinador puede suspender el estudio.

Lea las siguientes afirmaciones y marque la casilla apropiada abajo:

1) Estoy de acuerdo en participar en el examen del FHS, que incluye la recolección de datos, muestras de sangre, orina y varias pruebas de investigación y mediciones. Estoy de acuerdo en que se usen mis datos, muestras y materiales de investigación para los estudios de factores que contribuyen a enfermedades del corazón, los vasos sanguíneos, los pulmones y la sangre, accidentes cerebrovasculares, pérdida de memoria, cáncer y otras enfermedades y afecciones de salud.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 0*)

2) Estoy de acuerdo en permitir que mis datos, sangre, ADN y otro material genético, células iPS y sus derivados, muestras de orina y otros especímenes, sean utilizados en la investigación genética de los factores que contribuyen a enfermedades del corazón, los vasos sanguíneos, los pulmones y la sangre, accidentes cerebrovasculares, pérdida de memoria, cáncer y otras enfermedades y condiciones de salud.

   | _| SÍ | _| NO (*Para uso interno: código de oficina* 3)

3) Estoy de acuerdo en permitir que investigadores de empresas comerciales tengan acceso a mis datos, sangre, ADN y otro material genético, células iPS y sus derivados, muestras de orina y otros especímenes para investigación. Entiendo que mis datos y muestras se compartirán sin mi nombre o identificadores personales directos.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 4*)

4) Estoy de acuerdo en permitir que el FHS divulgue los resultados de los exámenes y las pruebas de investigación no-genéticas conmigo, mi médico, clínica, hospital u otro proveedor de atención médica.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 30*)

5) Estoy de acuerdo en permitir que el FHS me dé, y con mi permiso también a mi médico, clínica, hospital u otro proveedor de atención médica, información relacionada con la investigación genética referente a mí.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 31*)

Sujeto:_____
Nombre en letra de imprenta del sujeto

Al firmar este formulario de consentimiento, usted indica lo siguiente:

- Que ha leído este formulario (o se lo han leído).
- Que sus preguntas se han respondido a su entera satisfacción.
- Que usted acepta participar voluntariamente en este estudio de investigación.
- Que usted permite el uso y la divulgación de información que pueda identificarlo, según lo explicado, incluso su información de salud.

Para ser completado por el sujeto si firma personalmente

_____ _____
Firma del sujeto Fecha

Para ser completado por el representante legalmente autorizado (Legally Authorized Representative, LAR) si el sujeto no firma personalmente
Doy mi consentimiento en nombre del sujeto.

_____ _____
Nombre en letra de imprenta del representante legalmente autorizado (LAR) Relación con el sujeto

_____ _____
Firma del representante legalmente autorizado Fecha

Investigador:_____
Nombre en letra de imprenta de la persona a cargo del análisis del consentimiento

Para ser completado por el investigador si el sujeto firma personalmente
He explicado personalmente la investigación al sujeto mencionado anteriormente y he respondido todas sus preguntas. Considero que el sujeto comprende lo que implica el estudio y acepta libremente participar.

_____ _____
Firma de la persona a cargo del análisis del consentimiento Fecha

Para ser completado por el investigador si el sujeto no firma personalmente
He explicado personalmente la investigación al representante legalmente autorizado del sujeto mencionado anteriormente y he respondido todas sus preguntas. Considero que el representante legalmente autorizado del sujeto comprende lo que implica el estudio y acepta libremente que el sujeto participe.

Considero que el sujeto mencionado anteriormente (marque una opción):
☐ Es capaz de comprender lo que implica el estudio y acepta libremente participar.
☐ No es capaz de comprender lo que implica el estudio.

_____ _____
Firma de la persona a cargo del análisis del consentimiento Fecha

Framingham Heart Study
Offspring Exam 10, Omni 1 Exam 5
RESEARCH CONSENT FORM

Welcome Back to the Framingham Heart Study

Together we are helping to fight heart disease and other major diseases and health conditions through research.

Basic Information

Title of Project: Framingham Heart Study

IRB Number: H-32132

Sponsor: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)

Principal Investigator: [redacted] Avenue, Suite 2 [redacted]

[redacted]

[redacted]

Why is the research study being done?

The Framingham Heart Study is a long-term research study. The purpose of the study is:

(1) To help understand how heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other major diseases and health conditions develop; and

(2) To examine DNA and its relationship to the risks of developing these diseases and other health conditions.

The research examination that will be conducted as part of this study is not clinical care. The tests are for research purposes only. We do not provide medical services. This research examination does not take the place of medical care by your own health care provider.

About your consent

Please read this research consent form carefully. It tells you important information about the research study. Taking part in a research study is voluntary. The decision whether or not to take part in all or any part of the research exam is entirely up to you. If you choose to take part, you

can decide to stop at any time. Your decision will be honored and respected. There will be no penalty to you if you decide to stop or not to take part.

If I have questions or concerns about this research study, whom can I call?

If you have any questions about the research or about this form, please ask us. You can call us with your questions or concerns. You can ask questions as often as you want.

[redacted]

The Framingham Heart Study is led by investigators from Boston University and the National, Heart, Lung, and Blood Institute at the National Institutes of Health. Dr. Vasan S Ramachandran and Dr. Daniel Levy are in charge of the research study. You can contact Dr. Ramachandran at (617) 358-1310 Monday through Friday between 9am and 5pm or by email at vasan@bu.edu and Dr. Daniel Levy at (508) 935-3400 Monday to Friday between 9am and 5pm or by email at levyd@nih.gov.

You may also call 617-358-5372 or email medirb@bu.edu. You will be talking to someone at the Boston Medical Center and Boston University Medical Campus IRB. The IRB is a group that helps monitor research. You should call or email the IRB if you want to find out about your rights as a research subject. You should also call or email if you want to talk to someone who is not part of the study about your questions, concerns, or problems.

What will happen in this research study?

You will need to fast for 10 hours before you come to the study appointment for the blood draw. You can continue to drink water while fasting and take your usual medication on the morning of your visit.

Your research examination will take place at the FHS Research Center at 73 Mount Wayte Avenue, Framingham, MA, by phone or video conference (also referred to as a televisit), or in your home or other residence. The full onsite research exam will take around 4-5 hours to complete or the exam may also be split into multiple pieces: a 2-hour televisit and 2.5 hour in-person visit at the Research Center. Exam components that may be completed remotely will be included during the televisit and components that require in-person assessment will be conducted at the Research Center or offsite home or other residence.

As before, we will

- draw a sample of blood for genetic and laboratory tests to better understand risk factors for heart disease and other diseases under investigation (for example, the amount and function of different types of cholesterol in your blood). The total blood draw will be up to 80mL, which is about 5.4 tablespoons. The blood draw will occur soon after your arrival.
- collect a urine sample
- measure your height, weight, and waist
- measure grip strength
- complete an electrocardiogram (ECG)
- record your blood pressure
- update your medical history information

- complete a test of cardiac vascular function (tonometry) that examines heart function using ultrasound scanning (echocardiogram) and tests blood vessel (artery) stiffness by recording the blood pressure and flow waveforms
- ask you to sign a form to allow FHS to obtain copies of medical records, including Medicare records. The release form is valid to obtain these records unless canceled by you.
- contact you later by mail, email, or by phone (call or text) to obtain additional information or to invite you to participate in further FHS related studies. You may also be invited to return for another examination in the future.

Surveys
We will also be asking you to complete questionnaires such as physical function, diet, exercise, memory and mood, and your lifestyle habits, including whether you smoke or use alcohol. Some of the questionnaires you will have seen before and others will be new to you.

Some of your responses will be recorded using a digital audio recorder. Recordings will be analyzed in conjunction with other study information. We will also use recordings to make sure that your responses are accurately documented.

There are some new research activities.

1. Fibroscan: We are interested in improving our understanding of the factors that can help predict the development of liver fat and liver fibrosis (scarring) for this study, you will have a test called a Fibroscan. The Fibroscan measures the presence of fat or scarring in the liver. A painless pulse is generated on your skin that travels to the liver and measures how stiff your liver is.

   What risks can I expect? There may be minor discomfort from the application of lubricating jelly and pressure on the skin from the Fibroscan probe. However, there are no known risks associated with the Fibroscan.

   There are some conditions that may interfere with the ability of the device to obtain valid measures. They include being pregnant, having fluid in the abdominal cavity (ascites), and having implanted medical devices, such as a heart pacemaker. We will ask you to confirm if you have any of these conditions and if you do, we will not complete the Fibroscan.

2. Pain Assessment Study: We are interested in learning about pain people may be experiencing in their daily lives, and to better understand why some people have pain, more pain, or pain in more parts of their body, than other people do. We will ask some questions about pain and assess your sensitivity to pressure on your skin. To test your sensitivity to pressure, a small device will be pressed against a muscle on your shoulder to measure how much pressure is applied before you feel any discomfort.

   What risks can I expect? Although rare, there is the potential for skin irritation and redness or bruising during testing. Bruising or discomfort could potentially result from application of the pressure meter during pressure pain threshold testing and/or blood pressure cuff inflation.

3. Brain Health Study: We are interested in finding a way to define brain health beyond the evaluation of cognitive testing. We will ask you to participate in a number of sensory

motor tests that capture your brain health, including testing your vision, hearing, and motor function. You will have eye testing (without dilatation); hearing testing (using an iPad and headphones); and physical function testing (includes gait speed assessment on an electronic gait mat, during normal walk and while doing a mental task like counting and timed chair stands).

What risk can I expect? There are no risks involved in eye and hearing testing. Gait testing has a minimal risk of falling. All precautions will be taken to prevent falls. A study staff member will stand near you to prevent you from falling and help you if needed.

4. Electronic FHS (eFHS) Study: If you live in the US, have an email account with access to a daily Internet connection or have a smartphone, we will invite you to take part in the eFHS study. Taking part requires that you visit a web platform, download apps and use wireless devices. The apps will require you to complete surveys regarding lifestyle and health, and the devices will measure heart rate, blood pressure, weight, and physical activity.

   What risks can I expect? There are no known risks to taking part in this study.

5. Bone Scan: We are interested in learning about how the skeleton changes with aging. We will ask you to participate in two bone scans to examine the bone structure in your lower leg and lower arm. The scan is a non-invasive and painless test, and provides a detailed image of the "micro-architecture" inside the bone. Each scan takes about two minutes and requires that you keep as still as possible.

   What risks can I expect? Bone scans involve the use of x-rays, a form of energy also called radiation. The radiation dose for the two scans together will be less than 10 μSv, which is equivalent to 2-3 days of background radiation that individuals experience in the U.S. Since the amount of radiation from the bone scans is so small, there are no known long-term effects of this radiation on your health.

Some of the study components described in this section "What will happen in this research study?" may not be administered during televisits, due to the need to take certain measurements in person. Also, some of the study components may not be administered during offsite examinations taking place at your home or care facility, due to large equipment that cannot be transported outside of the research center. For example, Fibroscan, Tonometry, and Computed Tomography.

Overall Examination Risks and Discomforts
General Risks: The research exam is time consuming and repetitive. Other discomforts include headaches, feeling hungry due to fasting, fatigue and chill during the visit.

CT bone scans involve exposure to radiation. Since the amount of radiation is so small, equivalent to 2-3 days of background radiation there are no known long-term effects of this radiation on your health. However due to potential risk to a fetus, pregnant women, as determined by self-report or by a positive pregnancy test, will be excluded from this test.

We do not expect any risk of injury as a result of your participation in the study. However, first aid will be available.
Unknown Risks: There may also be some risks that we are unable to determine at this time.

Genetic Studies

You may have already provided consent for the collection of biological samples for DNA research or the creation of Induced Pluripotent Stem Cells (iPS cells). We plan to continue to do genetic research on the DNA from your biological samples. The biological samples include blood cells, tissue cells, etc. DNA is the material that makes up your genes. Genes are passed from parent to child. All living things are made of cells. Genes are the part of cells that contain the instructions which tell our bodies how to grow and work and determine physical characteristics such as hair and eye color.

Also, if you agree, we will process white blood cells from a sample of your blood to become stem cells in the laboratory. The resulting cells are known as Induced Pluripotent Stem Cells (iPS cells), and they will be used in the laboratory to act like cells from other organs, such as liver cells, fat cells, heart cells, lung cells, vascular cells, gut cells, nerve cells, different types of blood cells, and many other engineered or naturally occurring cell types. These cells and the cell products that can be obtained from them such as RNA, proteins, and metabolites may be studied in laboratories to learn more about the causes of health and diseases of these organs.

Your cells will be stored indefinitely in a stem cell repository at Boston University. Your cells may also be stored in a central repository or bank.

If you agree, your stored tissues, cells and any resulting iPS cell lines or their derivatives could be used in future related and unrelated research studies including:

- Injecting or transplanting the stem cells or their derivatives into animals for research purposes. Your samples may be used in research that involves genetic manipulation but they will not be used to clone or to otherwise create an entire human being.
- Testing for genetic and DNA composition. Genes may be analyzed and/or manipulated to study normal function or development, and some of the DNA in the stem cells or their derivatives may be altered.
- Other uses involving research or development of commercial products for the diagnosis, prevention, or treatment of various diseases.
- Samples (blood cells, the iPS cells, or their derivatives) obtained from you in this study may be used in the development of one or more diagnostic or therapeutic products which could be patented and licensed by those involved in the research or development of such products. There are no plans to provide financial compensation to you should this occur.

How will I learn the results of this study?

The main way results of research from this study are reported is in scientific publications and presentations at scientific meetings. Summary findings are also sometimes described in our newsletters and on our study website.

We will also report some routine research test measurements to you and/or your health care provider at the time of the exam or after your visit. These may include, for example, blood pressure and cholesterol.

In some cases, if we determine it to be appropriate, we may report to you and/or your health care provider research findings as they relate to you, if you give your permission. This information, if it is reported, might be reported long after your visit for a number of reasons. As an example, it might take years of work to analyze information and arrive at research findings, possibly using newly developed scientific methods.
Our genetic research might generate findings that could be relevant to you and possibly your family members, such as information about a particular genetic variant that might put you at risk of a serious health condition. At this time, we believe that most of the genetic research findings do not have medical importance to individuals, but the field of genetics is changing rapidly.

We currently do not have specific plans to contact you or your health care provider about genetic or non-genetic research findings other than some routine research test measurements. In general, we cannot commit to providing any other research findings to you. In determining whether we share additional research information with you, we will take into account a number of considerations on a case-by-case basis. These might include whether the findings were based on tests that are clinically acceptable, accurate and reliable, whether the findings reveal a significant risk of a serious health condition, whether there is, at the relevant time, a recognized treatment or prevention intervention or other available actions that have the potential to change the clinical course of the health condition, whether reporting or not reporting the results is likely to increase the risk of harm to you, and other relevant factors that we might not be able to predict at this time. In the cases when genetic research findings are reported to you, a study investigator and genetic counselor will contact you to confirm your continued interest in hearing about genetic research results. If you confirm your interest, the study staff will inform you of the research results and recommend next steps such as obtaining confirmatory clinical testing and speaking with your personal healthcare provider.

Research test measurements and findings are not the same as clinical test results. As such, our research examination is not necessarily performed by individuals with clinical training and qualifications, and many parts of the examination do not meet the standards for certified clinical testing. For these reasons, our research tests should not be relied on to make any diagnosis, treatment, or health planning decisions. We do not provide health care or give medical advice or genetic testing or provide counseling. If you or your health care provider decides that follow-up tests or treatments are necessary, then you (or a third party such as a health insurance carrier or Medicare) will be responsible for the cost.

How are my samples and information shared with other researchers?

Samples and information will be kept indefinitely. If you agree, your data and donated blood, blood cells, resulting iPS cells or their derivatives, urine, and any other specimens may be shared with other researchers. These include other academic, non-profit, and for-profit entities, including but not limited to hospitals, universities, cell/tissue storage banks and repositories, databanks and data repositories and businesses, whether for related or unrelated research studies. The cell/tissue storage banks and repositories, databanks and data repositories, include but are not limited to, NIH repositories dbGaP and BioLINCC. Internal and external researchers may request data and materials for research. The repositories have standard operating procedures to protect your confidentiality. Your data and samples will not be labeled with your name or other direct personal identifiers, only a code.

Coded audio recording information will be analyzed by qualifying collaborators inside and outside of BUMC. Your name and other direct personal identifiers will not be shared with these entities.

You have the right to refuse to allow your data and samples to be used or shared for further research. Please check the appropriate box in the selection below.

If you give your permission to allow your data and biological samples to be used or shared for further research, you may withdraw your permission at any time by contacting the FHS investigators. However, if your data or samples have already been released to other researchers, we will not be able to instruct the other researchers to stop using them, to destroy them or products made from them. Your data and samples will not include your name or other direct identifiers.

What risks can I expect?

General risks and individual risks related to new activities are discussed above.

Participating in genetic research could have a negative impact on you, your family, and your loved ones. The genetic studies might result in research findings that relate to your risk of a serious health condition or other genetic information that we might consider to be appropriate to report to you and your health care provider, if you wish us to report them (see below). This could present you with some difficult decisions regarding the available information and the disease risks you and your family members might face. Knowledge of genetic research findings can provoke anxiety and influence decisions regarding marriage, family planning, and other matters. There is a potential risk that your genetic information could be used to your disadvantage. For example, if genetic research findings suggest a serious health problem, that could be used to make it harder for you to get or keep a job or insurance. Both Massachusetts state laws and federal laws, particularly the Genetic Information Nondiscrimination Act (GINA), generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. These laws will generally protect you in the following ways:

1. Health insurance companies and group health plans may not request your genetic information that we get from this research.
2. Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
3. Massachusetts employers with 6 or more employees (or 15 or more employees in other states, under GINA) may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that neither Massachusetts law nor GINA protects you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Thus, life insurance, disability insurance, and long-term care insurance companies may legally ask whether you have had genetic testing and deny coverage for refusal to answer this question.

How is my information protected?

We will store your information in ways we think are secure. We label your samples and information with a code, and we keep the key to the code in a password protected database.

Only approved staff is given the password. We use other safeguards at our facilities and for our information technology and systems to protect the privacy and security of your information.

We do not sell, rent, or lease your contact information.

If information from this study is published or presented at scientific meetings, and when your samples and information are shared with other researchers and deposited in data and specimen banks and repositories, your name and other direct personal identifiers will not be used.

However, we cannot guarantee total privacy. We may provide access to your information in order to do the study and to make sure we do the study according to certain standards set by ethics, law, and quality groups. Information may be made available to researchers that are part of this study, the Institutional Review Board that oversees this research, research and non-research staff and organizations who need the information to do their jobs for the conduct and oversight of the study, people or groups that we hire to do work for us (such as data or biosample storage companies, insurers, and lawyers), and Federal and state agencies as required by law or if they are involved in the research or its oversight. In most cases, any information that is given out to others is identified by code and not with your name or other direct personal identifiers. Once information is given to outside parties, we cannot promise that it will be kept private. Please be aware that your personal information may be given out if required by law (e.g., to prevent possible injury to yourself or others).

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. All studies funded by the National Institutes of Health that involve identifiable information or biological samples are covered by a CoC. The CoC provides how we can share research information or biological samples. Because we have a CoC, we cannot give out research information or biological samples that may identify you to anyone that is not involved in the research except as we describe below. Even if someone tries to get your information or biological samples in connection with a legal proceeding, we cannot give it to them. The CoC does not prevent you from sharing your own research information.

If you agree to be in the study and sign this form, we will share information and biological samples that may show your identity with the following groups of people:

- People who do the research or help oversee the research, including safety monitoring.
- People from Federal and state agencies who audit or review the research, as required by law. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health.
- Investigators who will get your data and your biological samples as we described in the section "*What will happen in this research study?"* These people are expected to protect your information and biological samples in the same way we protect it.
- Any people who you give us separate permission to share your information.

You should know that we are required to report information about child abuse or neglect; elder abuse; specific reportable diseases; or harm to others.

We will share research data where we have removed anything that we think would show your identity. There still may be a small chance that someone could figure out that the information is about you. Such sharing includes:

- Publishing results in a medical book or journal.

- Adding results to a Federal government database
- Using research data in future studies, done by us or by other scientists.
- Using biological samples in future studies, done by us or by other scientists.

Samples that are collected from you in this study will be analyzed to find out information about your genetic makeup. Your genetics and health information, without your name or other data that could easily identify you, will be put in a database run by the National Institutes of Health (NIH). This may include your whole genome information. Other researchers can ask the NIH to get your information from the database. You should know that it is possible that your genetics information might be used to identify you or your family, though we believe it is not too likely that this will happen. Once your information is given to the NIH database, you can ask to have NIH stop sharing it, but NIH cannot take back information that was already shared.

Patenting Discoveries

Research from this study may, one day, result in new tests to diagnose or predict diseases. It may also lead to the development of new ways to prevent or treat diseases. As is true of all federally-funded research, researchers and their employers are permitted by Federal law to patent discoveries from which they may gain financially. You and your heirs will not benefit financially.

What are the possible benefits from being in this research study?

While you will not receive any direct benefit as a result of your participation in this study; we hope that this study will help us better understand what causes heart disease and other diseases and conditions and how to better prevent and treat them.

What are the costs of taking part in the study?

Costs that you may incur on the day of your participation include, but are not limited to, loss of work and transportation costs (gas, tolls, etc.).

You will not be paid for your participation in this study.

No special arrangement will be made by the Framingham Heart Study for compensation or payment solely because of your participation in this study. If you think you have been injured by being in this study, please let the investigators know right away. Boston University and the sponsors do not offer a program to provide compensation for the cost of care for research related injury or other expenses such as lost wages, disability, pain, or discomfort. You will be sent a bill for the medical care you receive for research injury if your medical insurance does not pay for your medical care. This does not waive any of your legal rights.

How long will I be in the study?

FHS is a long-term study.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

The investigator may decide to discontinue your participation without your permission because he/she may decide that staying in the study will be bad for you, or the sponsor may stop the study.

Please read the following statements and check the appropriate box below:

1) I agree to participate in the FHS examination, including the collection of data, blood, urine samples, and various research tests and measurements. I agree to the use of all data, samples, and research materials for studies of the factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other diseases and health conditions.

   | _| YES | _| NO (*For Internal Use - Office Code 0*)

2) I agree to allow my data, blood, DNA and other genetic material, iPS cells and their derivatives, urine samples, and any other specimens to be used in genetic research, of factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other diseases and health conditions.

   | _| YES | _| NO (*For Internal Use - Office Code* 3)

3) I agree to allow researchers from commercial companies to have access to my data, blood, DNA and other genetic material, iPS cells and their derivatives, urine samples, and any other specimens for research. I understand that my data and specimens will be shared without my name or direct personal identifiers.

   | _| YES | _| NO (*For Internal Use - Office Code 4*)

4) I agree to allow the FHS to release the findings of non-genetic research tests and examinations to me and/or my physician, clinic, hospital, or other health care provider.

   | _| YES | _| NO (*For Internal Use - Office Code 30*)

5) I agree to allow the FHS to provide me, and with my permission, my physician, clinic, hospital, or other health care provider information relating to genetic research findings as they may relate to me.

   | _| YES | _| NO (*For Internal Use - Office Code 31*)

Subject: _____
Printed name of subject

By signing this consent form, you are indicating that

- you have read this form (or it has been read to you)
- your questions have been answered to your satisfaction
- you voluntarily agree to participate in this research study
- you permit the use and sharing of information that may identify you as described, including your health information.

To be completed by subject if personally signing

_____ _____
Signature of subject Date

To be completed by LAR if subject does not personally sign
I am providing consent on behalf of the subject.

_____ _____
Printed name of Legally Authorized Representative (LAR) Relationship to Subject

_____ _____
Signature of Legally Authorized Representative Date

Researcher: _____
Printed name of person conducting consent discussion

To be completed by researcher if subject personally signs
I have personally explained the research to the above-named subject and answered all questions. I believe that the subject understands what is involved in the study and freely agrees to participate.

_____ _____
Signature of person conducting consent discussion Date

To be completed by researcher if subject does not personally sign
I have personally explained the research to the above-named subject's Legally Authorized Representative and answered all questions. I believe that the Legally Authorized Representative understands what is involved in the study and freely agrees to have the subject participate.

I consider that the above-named subject (check one):
☐ is capable of understanding what is involved in the study and freely agrees to participate.
☐ is not capable of understanding what is involved in the study.

_____ _____
Signature of person conducting consent discussion Date

Framingham Heart Study
Offspring Exam 10, Omni 1 Exam 5
Brain Health Study

RESEARCH CONSENT FORM ADDENDUM

Basic Information

Title of Project: Multidimensional Assessment of Brain Health as a Marker of Dementia Risk and Resilience

IRB Number: H-40757

Sponsor: National Institute on Aging (NIA), National Institutes of Health (NIH)

Principal Investigator: Sudha Seshadri, MD [redacted]

Please take time to review this information carefully. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Voluntary Participation - You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are entitled.

The PI of the Brian Health Study is Dr. Sudha Seshadri who is Professor of Neurology at the University of Texas Health Sciences Center, San Antonio, TX and also an adjunct Professor of Neurology at Boston University School of Medicine. [redacted]

Overview of the Brain Health Study
We are interested in finding a way to define brain health beyond the evaluation of cognitive testing. We will ask you to participate in a number of sensory motor tests that capture your brain health, including testing your vision, hearing, and motor function. You will have eye testing (without dilatation); hearing testing (using an iPad and headphones); and motor function testing (includes gait speed assessment on an electronic gait mat, during normal walk and while doing a mental task like counting.) As described in the main consent form, we may also report some routine research test measurements to you and/or your health care provider at the time of the exam or after your exam

The Brain Health Study within the Framingham Heart Study Offspring Exam 10, Omni 1 Exam 5 is conducted in collaboration with The University of Texas Health Science Center at San Antonio.

All procedures described below will be performed for research purposes only.
A. Vision Testing:

Optical Coherence Tomography Angiography (OCTA):
This exam will be performed without dilating eye drops. You will be asked to rest your chin and forehead on a support that is attached to the OCT machine. You will be asked to fixate your eyes on a target for a few moments and as a camera scans and takes images of the retina, the back of your eye. It also measures blood flow in the eye and is a completely non-invasive measurement that is approved by the U.S. Food and Drug Administration (FDA) as a rapid method of assessing retinal capillary density

B. **Motor Testing**

In ***Gait Testing***, you will be asked to walk on a gait mat (that appears like a regular rug or mat) that has pressure sensors below it. A computer and software connected to the mat will capture the different aspects of the walk including speed, step length, step width, etc. You will be asked to walk at your usual pace, fast pace and while doing cognitive tasks like counting backwards.

C. Hearing Testing
Using a portable tablet-based system and earphones we will present a **pure tone** to the **ear** measuring the lowest intensity in decibels (dB) at which this **tone** is perceived 50% of the time. This measurement is called **threshold**.

Risks of Participation in this research

Informational risks related to the study
Your data will be assigned a code number. Your name, medical record number, or other information that easily identifies you will not be stored with your samples or data. The key that links your identifying information to the code number will be stored securely in a separate file and will not be shared with researchers that are not part of our study team.
The main risk of allowing us to use your data for research is a potential loss of privacy. This risk is serious but rare because we take many steps to protect your information. We protect your privacy by coding your data and removing personal identifiers. Research results obtained in this study will not be placed in your medical record unless we contact you with a finding of high medical importance. We do not think that there will be further risks to your privacy by sharing your data with other researchers; however, we cannot predict how this data will be used in the future.

Risks of Study Procedures
There is also minimal risk of falling during the gait testing, but we will take the same precautions described above to prevent falls by walking behind and to the side and assisting if required.

For more information about risks and side effects, ask one of the researchers or study staff. We will tell you about any significant new findings which develop during the course of this research which may relate to your willingness to continue taking part.

What if a research-related injury occurs?
The researchers have taken steps to minimize the known or expected risks and we expect no injuries from these studies. However, you may still experience problems or side effects, even though the researchers are careful to avoid them. in the event of a research-related injury or if you experience an adverse reaction, please immediately contact study staff. See the section "Contact Information" for phone numbers and additional information. You may also need to tell your regular doctors.

If you are injured or made sick from taking part in this research study, medical care will be provided. This care may be billed to you or your insurance. Depending on the circumstances, this care may be provided at no cost to you. We do not offer a program to provide compensation for the cost of care for research related injury. The study staff can provide you with more information.

If you sign this form, you do not give up your right to seek additional compensation if you are harmed as a result of being in this study

Information about how this study will use your Protected Health Information (PHI)
Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of monitoring research may want to see study records which identify you as a subject in this study.

Research policies require that private information about you be protected and this is especially true for your health information. However, the law sometimes allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study.

What is Protected Health Information (PHI)?
Protected Health Information is information about a person's health that includes information that would make it possible to figure out who the person is. According to the law, you have the right to decide who can see your protected health information. If you choose to take part in this research study, you will be giving your permission to the investigators and the research study staff (individuals carrying out the study) to see and use your health information for the study. In carrying out this research, the health information we will see and use about you will include:

- your medical history and blood work,
- results of eye, ear and gait assessment tests,
- information from interviews or from questionnaires,
- demographic information like your age, sex

We will get this information from the data collected today and over the years at the Framingham Heart Study

How will your PHI be protected?
In an effort to protect your privacy, the study staff will use code numbers instead of your name, to identify your health information. Initials and numbers will be used on any photocopies of your

study records, and other study materials containing health information that are sent outside the institutions listed above for review or testing. If the results of this study are reported in medical journals or at meetings, you will not be identified.

Parts of your PHI may be photocopied and sent to a central location or it may be transmitted electronically, such as by e-mail, fax, or other secure means of transmission. The groups receiving your health information may not be obligated to keep it private. They may pass information on to other groups or individuals not named here.

How will your PHI be shared with other Researchers?
Because it is research, we will be unable keep your PHI completely confidential. We may share your health information with people and groups involved in conducting and overseeing this research study including:

- the following collaborators at other institutions that are involved with the study: The University of Texas Health Science Center at San Antonio, Boston University School of Medicine, Massachusetts Eye and Ear Infirmary and University of Southern California
- the members of the local research team;
- the Institutional Review Board and the Compliance Office of the University of Texas Health Science Center at San Antonio, and other groups that oversee how research studies are carried out; and
- the Research offices at the University of Texas Health Science Center at San Antonio

If you decide to participate in this study, you will be giving your permission for the groups named above, to collect, use and share your health information for research purposes. If you choose not to let these groups collect, use and share your health information as explained above, you will not be able to participate in this research study.

Do you have to allow the use of your health information?
You do not have to allow (authorize) the researchers and other groups to see and share your health information. If you choose not to let the researchers and other groups use your health information, there will be no penalties, but you will not be allowed to participate in the Brain Health Study portion part of the Framingham Heart Study Examination.

After you enroll in this study, you may ask the researchers to stop using your health information at any time. However, you must provide this in writing and send your letter to ***Vasan Ramachandran, Principal Investigator, Framingham Heart Study, 73 Mt Wayte Ave, Suite 2, Framingham, MA 01702.*** If you tell the researchers to stop using your health information, your participation in this part of the Framingham Heart study will end and the study staff will stop collecting new health information from you and about you for this study. However, the study staff will continue to use the health information collected up to the time they receive your letter asking them to stop.

Can you ask to see the PHI that is collected about you for this study?
The federal rules say that you can see the health information that we collect about you and use in this study. Contact the study staff if you have a need to review your PHI collected for this study. If you ask for research information that is not in your medical record, we might not

provide it to you, but we will explain why not. You may use the contact information on the first page of this form to find out how to get your health information.

How long will your PHI be used?
By signing this form, you agree to let us use and disclose your health information for purposes of the study until the end of this study; at this time we do not have any specific end date and will continue using your data until it is no longer of scientific value.

Contact Information
If you have questions now, feel free to ask us. If you have additional questions later or you wish to report a problem or complaint which may be related to this study please contact:

[redacted]

Research Consent & Authorization Signature Section

If you agree to participate in this research and agree to the use of your protected health information in this research sign this section. You will be given a signed copy of this form to keep. You do not waive any of your legal rights by signing this form.

SIGN THIS FORM ONLY IF THE STATEMENTS LISTED BELOW ARE TRUE

- You have read the above information.
- Your questions have been answered to your satisfaction.

Adult Signature Section

- You have voluntarily decided to take part in this research study.
- You authorize the collection, use and sharing of your protected health information as described in this form.

Printed Name of Subject	Signature of Subject	Date

Surrogate Signature Section

- You are voluntarily giving your consent for another person to participate in this study because you believe this person would want to take part if able to make the decision and you believe it is in this person's best interest.
- You are authorizing the collection, use and sharing of another person's protected health information as described in this form.

Printed Name of Subject	Signature of **Subject**, indicating Assent *(If incapable of signing, person obtaining consent should initial here)*	Date
Printed Name of Legally Authorized Representative (LAR)	Signature of Legally Authorized Representative (LAR)	Date

Researcher

Printed Name of Person Obtaining Consent and Authorization	Signature of Person Obtaining Consent & Authorization	Date

BMC and BU Medical Campus IRB
IRB NUMBER: H-32132
IRB APPROVAL DATE: 07/21/2021

Framingham Heart Study
Offspring Exam 10, Omni 1 Exam 5
Bone Study Informed Consent Form ADDENDUM

Basic Information

Title of Project: Framingham Heart Study

IRB Number: H-32132

Sponsor: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH)

Principal Investigator: Vasan S. Ramachandran, MD

[redacted]

Study Phone Number: [redacted]

[redacted]

Overview of the Bone Study at the Framingham Heart Examination

We are interested in learning about how the skeleton changes with aging. We will ask you to participate in two bone scans to examine the bone structure in your lower leg and lower arm. The scan is a non-invasive and painless test, and provides a detailed image of the "micro-architecture" inside the bone. Each scan takes about two minutes and requires that you keep as still as possible.

The research examination that will be conducted as part of this study is not clinical care. The tests are for research purposes only. We do not provide medical services. This research examination does not take the place of medical care by your own health care provider.

About your consent

Please read this research consent form carefully. It tells you important information about the research study. Taking part in a research study is voluntary. The decision whether or not to take part in all or any part of the research exam is entirely up to you. If you choose to take part, you can decide to stop at any time. Your decision will be honored and respected. There will be no penalty to you if you decide to stop or not to take part.

If I have questions or concerns about this research study, whom can I call?

If you have any questions about the research or about this form, please ask us. You can call us with your questions or concerns. You can ask questions as often as you want.

[redacted].

The Framingham Heart Study is led by investigators from Boston University and the National, Heart, Lung, and Blood Institute at the National Institutes of Health. Dr. Vasan S Ramachandran and Dr. Daniel Levy are in charge of the research study. You can contact [redacted] You will be talking to someone at the Boston Medical Center and Boston University Medical Campus IRB. The IRB is a group that helps monitor research. You should call or email the IRB if you want to find out about your rights as a research subject. You should also call or email if you want to talk to someone who is not part of the study about your questions, concerns, or problems.

Overall Examination Risks and Discomforts
Bone scans involve the use of x-rays, a form of energy also called radiation. The radiation dose for the two scans together will be less than 10 μSv, which is equivalent to 2-3 days of background radiation that individuals experience in the U.S. Since the amount of radiation from the bone scans is so small, there are no known long-term effects of this radiation on your health. However due to potential risk to a fetus, pregnant women, as determined by self-report or by a positive pregnancy test, will be excluded from this test.

We do not expect any risk of injury as a result of your participation in the study. However, first aid will be available.

Unknown Risks: There may also be some risks that we are unable to determine at this time.

How is my information protected?

We will store your information in ways we think are secure. We label your samples and information with a code, and we keep the key to the code in a password protected database. Only approved staff is given the password. We use other safeguards at our facilities and for our information technology and systems to protect the privacy and security of your information.

We do not sell, rent, or lease your contact information.

If information from this study is published or presented at scientific meetings, and when your samples and information are shared with other researchers and deposited in data and specimen banks and repositories, your name and other direct personal identifiers will not be used.

However, we cannot guarantee total privacy. We may provide access to your information in order to do the study and to make sure we do the study according to certain standards set by ethics, law, and quality groups. Information may be made available to researchers that are part of this study, the Institutional Review Board that oversees this research, research and non-research staff and organizations who need the information to do their jobs for the conduct and oversight of the study, people or groups that we hire to do work for us (such as data or biosample storage companies, insurers, and lawyers), and Federal and state agencies as required by law or if they are involved in the research or its oversight. In most cases, any information that is given out to others is identified by code and not with your name or other direct personal identifiers. Once information is given to outside parties, we cannot promise that it

will be kept private. Please be aware that your personal information may be given out if required by law (e.g., to prevent possible injury to yourself or others).

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. All studies funded by the National Institutes of Health that involve identifiable information or biological samples are covered by a CoC. The CoC provides how we can share research information or biological samples. Because we have a CoC, we cannot give out research information or biological samples that may identify you to anyone that is not involved in the research except as we describe below. Even if someone tries to get your information or biological samples in connection with a legal proceeding, we cannot give it to them. The CoC does not prevent you from sharing your own research information.

If you agree to be in the study and sign this form, we will share information and biological samples that may show your identity with the following groups of people:

- People who do the research or help oversee the research, including safety monitoring.
- People from Federal and state agencies who audit or review the research, as required by law. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health.
- Investigators who will get your data and your biological samples as we described in the section "*What will happen in this research study?"* These people are expected to protect your information and biological samples in the same way we protect it.
- Any people who you give us separate permission to share your information.

You should know that we are required to report information about child abuse or neglect; elder abuse; specific reportable diseases; or harm to others.

We will share research data where we have removed anything that we think would show your identity. There still may be a small chance that someone could figure out that the information is about you. Such sharing includes:

- Publishing results in a medical book or journal.
- Adding results to a Federal government database
- Using research data in future studies, done by us or by other scientists.
- Using biological samples in future studies, done by us or by other scientists.

Samples that are collected from you in this study will be analyzed to find out information about your genetic makeup. Your genetics and health information, without your name or other data that could easily identify you, will be put in a database run by the National Institutes of Health (NIH). This may include your whole genome information. Other researchers can ask the NIH to get your information from the database. You should know that it is possible that your genetics information might be used to identify you or your family, though we believe it is not too likely that this will happen. Once your information is given to the NIH database, you can ask to have NIH stop sharing it, but NIH cannot take back information that was already shared.

Patenting Discoveries

Research from this study may, one day, result in new tests to diagnose or predict diseases. It may also lead to the development of new ways to prevent or treat diseases. As is true of all federally-funded research, researchers and their employers are permitted by Federal law to

patent discoveries from which they may gain financially. You and your heirs will not benefit financially.

What are the possible benefits from being in this research study?

While you will not receive any direct benefit as a result of your participation in this study; we hope that this study will help us better understand what causes heart disease and other diseases and conditions and how to better prevent and treat them.

What are the costs of taking part in the study?

Costs that you may incur on the day of your participation include, but are not limited to, loss of work and transportation costs (gas, tolls, etc.).

You will not be paid for your participation in this study.

No special arrangement will be made by the Framingham Heart Study for compensation or payment solely because of your participation in this study. If you think you have been injured by being in this study, please let the investigators know right away. Boston University and the sponsors do not offer a program to provide compensation for the cost of care for research related injury or other expenses such as lost wages, disability, pain, or discomfort. You will be sent a bill for the medical care you receive for research injury if your medical insurance does not pay for your medical care. This does not waive any of your legal rights.

How long will I be in the study?

FHS is a long-term study.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

The investigator may decide to discontinue your participation without your permission because he/she may decide that staying in the study will be bad for you, or the sponsor may stop the study.

Subject: _____
Printed name of subject

By signing this consent form, you are indicating that

- you have read this form (or it has been read to you)
- your questions have been answered to your satisfaction
- you voluntarily agree to participate in this research study
- you permit the use and sharing of information that may identify you as described, including your health information.

To be completed by subject if personally signing

_____ _____
Signature of subject Date

To be completed by LAR if subject does not personally sign
I am providing consent on behalf of the subject.

_____ _____
Printed name of Legally Authorized Representative (LAR) Relationship to Subject

_____ _____
Signature of Legally Authorized Representative Date

Researcher: _____
Printed name of person conducting consent discussion

To be completed by researcher if subject personally signs
I have personally explained the research to the above-named subject and answered all questions. I believe that the subject understands what is involved in the study and freely agrees to participate.

_____ _____
Signature of person conducting consent discussion Date

To be completed by researcher if subject does not personally sign
I have personally explained the research to the above-named subject's Legally Authorized Representative and answered all questions. I believe that the Legally Authorized Representative understands what is involved in the study and freely agrees to have the subject participate.

I consider that the above-named subject (check one):
☐ is capable of understanding what is involved in the study and freely agrees to participate.
☐ is not capable of understanding what is involved in the study.

_____ _____
Signature of person conducting consent discussion Date

Estudio del Corazon de Framingham,
examen 10 de Offspring, examen 5 de Omni 1

FORMULARIO DE CONSENTIMIENTO PARA LA INVESTIGACIÓN

Bienvenido nuevamente al Estudio del Corazón de Framingham

Juntos estamos ayudando a combatir las enfermedades cardíacas y otras enfermedades y problemas de salud importantes mediante la investigación.

Información básica

Título del proyecto: Estudio del Corazón de Framingham

Número de la IRB: H-32132

Patrocinador: Instituto Nacional del Corazón, los Pulmones y la Sangre (National Heart, Lung, and Blood Institute, NHLBI), Institutos Nacionales de Salud (National Institutes of Health, NIH)

[redacted]

¿Por qué se está haciendo este estudio de investigación?

El Estudio del Corazón de Framingham es un estudio de investigación a largo plazo. Su propósito es el siguiente:

(1) ayudar a comprender cómo se desarrollan las enfermedades del corazón y los vasos sanguíneos, las enfermedades de los pulmones y la sangre, los accidentes cerebrovasculares, la pérdida de memoria, el cáncer y otras enfermedades y afecciones de salud importantes;

y

(2) examinar el ADN y su relación con los riesgos de desarrollar estas enfermedades y otras afecciones de salud.

El examen que se llevará a cabo como parte de este estudio de investigación no es igual a la atención médica en una clínica. Las pruebas son solo con fines de investigación. No ofrecemos servicios médicos. Este examen no reemplaza su control con su proveedor de atención médica.

Acerca de su consentimiento

Lea atentamente este formulario de consentimiento de investigación. Le brinda información importante sobre el estudio. La participación en un estudio de investigación es voluntaria. La decisión de participar o no, ya sea en parte o en la totalidad del examen, depende completamente de usted. Si usted elige participar, puede decidir dejar de hacerlo en cualquier momento. Su decisión será aceptada y respetada. No habrá ninguna sanción si decide no participar o dejar de participar.

¿A quién puedo llamar si tengo preguntas o dudas acerca de este estudio de investigación?

Si tiene alguna pregunta acerca de este estudio o de este formulario, consúltenos. Puede llamarnos por preguntas o dudas las veces que desee.

Puede llamar directamente a un miembro del personal del estudio al (508) 872-6562 o al (800) 854-7582, o puede enviar un correo electrónico a FHS@bu.edu.

El Estudiodel Corazón de Framingham es realizado por los investigadores de la Universidad de Boston, el Instituto Nacional Cardíaco, Pulmonar y Sanguíneo, y el Instituto Nacional de la Salud. El Dr. Vasan S. Ramachandran y el Dr. Daniel Levy están a cargo de la investigación. Puede comunicarse con el [redacted] comunicará con una persona del Centro Médico de Boston y de la Junta de Revisión Institucional (*Institutional Review Board*, IRB) del Campus Médico de la Universidad de Boston (Boston University Medical Campus, BUMC). La IRB es un grupo que ayuda a supervisar las investigaciones. Si desea conocer sus derechos como sujeto de una investigación, debe llamar o enviar un correo electrónico a la IRB. Comuníquese también con esta agencia si desea hablar sobre sus preguntas, inquietudes o problemas con una persona ajena a este estudio.

¿Qué sucederá en este estudio de investigación?

Usted deberá ayunar durante 10 horas antes de llegar a su cita debido a la muestra de sangre que tomaremos. Si toma algún medicamento en la mañana, hágalo como siempre. Puede continuar bebiendo agua durante el ayuno.

Su examen se llevará a cabo en el Centro de Investigación del Estudio del Corazón de Framingham (*Framingham Heart Study*, FHS) en 73 Mount Wayte Avenue, Framingham, MA, por teléfono o videoconferencia (también llamada *teleconsulta*), o en su casa u otra residencia. El examen completo en el lugar tomará alrededor de 4 a 5 horas. También se puede dividir en varias partes: 2 horas por teleconsulta y 2,5 horas por consulta en persona en el Centro de Investigación. Los componentes del examen que puedan completarse a la distancia se incluirán durante la teleconsulta y los que requieran una evaluación en persona se llevarán a cabo en el Centro de Investigación o en su casa u otra residencia.

Como en los exámenes anteriores:

- Tomaremos una muestra de sangre para pruebas genéticas y de laboratorio, para poder comprender mejor los factores de riesgo de enfermedades del corazón y otras enfermedades bajo estudio (por ejemplo, la cantidad y la función de diferentes tipos de colesterol en la sangre). La cantidad total de sangre extraída será alrededor de 80 ml, que son unas 5,4 cucharadas. La extracción de sangre

se realizará poco después de su llegada.
- Recolectaremos una muestra de orina.
- Mediremos su altura, peso y cintura.
- Mediremos la fuerza de agarre.
- Realizaremos un electrocardiograma (ECG).
- Mediremos su presión arterial.
- Actualizaremos su historia clínica.
- Haremos una prueba de la función vascular cardíaca (tonometría) que examina la función cardíaca mediante una ecografía (ecocardiograma) y evalúa la rigidez de los vasos sanguíneos (arterias) mediante el registro de la presión arterial y las formas de onda del flujo.
- Le pediremos que firme un formulario de consentimiento para que nos dé permiso de obtener copias de los expedientes médicos, incluidos los de Medicare. Este formulario será válido hasta que usted lo cancele.
- Lo contactaremos más adelante por correo, correo electrónico o por teléfono (llamada o mensaje de texto) para obtener información adicional o para invitarlo a participar en otros estudios relacionados con el FHS. También puede ser invitado a participar de nuevo a otro de nuestros exámenes.

Encuestas
También le pediremos que llene unos cuestionarios sobre, por ejemplo, la función física, dieta, ejercicio, memoria y estado de ánimo y sus hábitos de estilo de vida, incluyendo si fuma o consume alcohol. Algunos de los cuestionarios ya los ha hecho, otros serán nuevos para usted.

Algunas de sus respuestas se grabarán mediante una grabadora audio-digital. Las grabaciones serán analizadas junto con otra información del estudio. También usaremos las grabaciones para asegurarnos de que sus respuestas estén documentadas correctamente.

Hay algunas nuevas actividades de investigación.

1. Fibroscan: Estamos interesados en mejorar nuestra comprensión sobre los factores que pueden ayudar a predecir el desarrollo de grasa hepática y fibrosis hepática (cicatrización). Para este estudio, se le realizará una prueba llamada Fibroscan. El fibroscan mide la presencia de grasa o cicatrices en el hígado. Se genera un pulso sin dolor en la piel que viaja al hígado y mide su dureza.

   ¿Qué riesgos puedo esperar? Puede haber pequeñas molestias por la aplicación del gel y la presión sobre la piel con la punta del aparato fibroscan. Sin embargo, no hay riesgos conocidos asociados con el fibroscan.

   Hay algunas condiciones que pueden interferir con la capacidad del dispositivo para obtener medidas válidas. Estas incluyen las siguientes: estar embarazada, tener líquido en la cavidad abdominal (ascitis) y tener implantes médicos, como un marcapasos. Le pediremos que nos confirme si tiene alguna de estas condiciones para no realizar el fibroscan.

2. Estudio de evaluación del dolor: Estamos interesados en conocer sobre el dolor que las personas pueden experimentar en su vida diaria y comprender mejor por qué algunas personas sienten dolor y otras no o por qué unas personas sienten más dolor que otras, o por qué algunas personas sienten dolor en más partes del cuerpo que otras. Le haremos algunas preguntas sobre el dolor y evaluaremos su sensibilidad a la presión sobre la piel. Para evaluar su sensibilidad a la presión, se presionará un pequeño

dispositivo contra un músculo del hombro y se medirá cuánta presión se aplica antes de que sienta alguna molestia.

¿Qué riesgos puedo esperar? Aunque es poco común, existe la posibilidad de que se produzca irritación de la piel y enrojecimiento o hematomas durante la prueba. Es posible que aparezcan moretones o molestias por la aplicación del medidor de presión durante la prueba del umbral de dolor por presión o por el inflado del manguito del tensiómetro.

3. Estudio de salud del cerebro: Estamos interesados en encontrar otra forma distinta a la evaluación de las pruebas cognitivas para definir la salud del cerebro. Le pediremos que participe en una serie de pruebas motoras que capturarán la salud de su cerebro, que incluyen pruebas de la visión, audición y función motora. Se le realizará una prueba de ojos (sin dilatación); pruebas de audición (usando un iPad y auriculares); y pruebas de la función física (incluye la evaluación de la velocidad de la marcha en una alfombra electrónica, la evaluación durante la caminata normal y mientras se realiza una tarea mental, como contar, y la evaluación cronometrada de ponerse de pie desde una silla).

   ¿Qué riesgo puedo esperar? No existe ningún riesgo en las pruebas de ojos y audición. La prueba de la marcha tiene un riesgo mínimo de caída. Se tomarán todas las precauciones para evitar que esto ocurra. Un miembro del personal del estudio estará cerca de usted para evitar que se caiga y lo ayudará en caso de ser necesario.

4. Estudio electrónico del FHS (eFHS): Si vive en los Estados Unidos, tiene correo electrónico y acceso diario a Internet o un teléfono inteligente, lo invitamos a participar en el estudio eFHS. Para participar es necesario que ingrese a una plataforma web, descargue las aplicaciones y use dispositivos inalámbricos. Las aplicaciones requieren completar encuestas sobre salud y estilo de vida. Los dispositivos electrónicos miden la frecuencia cardíaca, presión arterial, peso y actividad física.

   ¿Qué riesgos puedo esperar? No existen riesgos conocidos por participar en este estudio.

5. Estudio del hueso: Estamos interesados en conocer cómo cambia el esqueleto con el envejecimiento. Le pediremos que participe en dos pruebas de densidad ósea para examinar la estructura ósea de la parte inferior de la pierna y el antebrazo. Es una prueba no invasiva e indolora y proporciona una imagen detallada de la "microarquitectura" del interior del hueso. Cada una dura aproximadamente dos minutos y requiere que se mantenga lo más quieto posible.

   ¿Qué riesgos puedo esperar? Las pruebas de densidad ósea implican el uso de rayos x, que son una forma de radiación. La dosis de radiación para los dos escaneos juntos será inferior a 10 µSv. Esto equivale a 2 o 3 días de radiación de fondo que experimentan las personas en los Estados Unidos. Debido a que la cantidad de radiación de las pruebas de densidad ósea es muy pequeña, no se conocen efectos a largo plazo en su salud por esta radiación.

Algunos de los componentes del estudio descritos en esta sección "¿Qué sucederá en este estudio de investigación?" no se puede administrar durante la teleconsulta, debido a la necesidad de realizar algunas mediciones en persona. Además, algunos de los exámenes del estudio no se pueden realizar fuera del Centro de Investigación, ni en su casa ni en un centro de atención, debido al tamaño del equipo necesario que imposibilita su traslado. Por ejemplo,

el fibroscan, la tonometría y la tomografía computarizada (TC).

Riesgos y malestares generales del examen
Riesgos generales: Este estudio lleva tiempo y es repetitivo. Otras molestias incluyen dolores de cabeza, sentirse con hambre debido al ayuno, tener fatiga y escalofríos durante la visita.

Las pruebas de densidad ósea por TC implican exposición a radiación. Debido a que la cantidad de radiación es muy pequeña, equivale a 2 o 3 días de radiación de fondo y no se conocen efectos a largo plazo en su salud por esta radiación. Sin embargo, debido al riesgo potencial para un feto, las mujeres embarazadas, según lo determinado por un autoinforme o por una prueba de embarazo positiva, serán excluidas de esta prueba.

No esperamos ningún riesgo de lesiones como resultado de su participación en el estudio. Sin embargo, tenemos disponibles primeros auxilios.

Riesgos desconocidos: Existe la posibilidad de otros riesgos que no hemos identificado hasta el momento.

Estudios genéticos
Es posible que ya haya otorgado su consentimiento para la recolección de muestras biológicas para la investigación del ADN o la creación de células madre con pluripotencialidad inducida (*Induced Pluripotent Stem Cells*, células iPS). Planeamos continuar realizando investigaciones genéticas con el ADN de sus muestras biológicas, las cuáles incluyen células sanguíneas, células de los tejidos, etc. El ADN es el material con el que están hechos sus genes. Los genes pasan del padre y la madre al hijo. Todos los seres vivos están compuestos de células. Los genes son la parte de las células que contienen las instrucciones para decirle a nuestro cuerpo cómo crecer y trabajar, y determinar sus características físicas, como cabello y color de ojos.

También, si está de acuerdo, en un laboratorio, procesaremos las células blancas de la sangre de una de sus muestras para convertirlas en células madre. Las células resultantes son conocidas como *células madre con pluripotencialidad inducida* (células iPS) y se utilizan en el laboratorio para que actúen como células de otros órganos; tales como células del hígado, células grasas, células del corazón, células pulmonares, vasculares, intestinales, células nerviosas, diferentes tipos de células sanguíneas y muchos otros tipos de células naturales. Estas células y los productos celulares que pueden obtenerse de ellas, tales como ARN, proteínas y metabolitos, pueden ser estudiados en laboratorios para aprender más sobre las causas de la salud o enfermedad de estos órganos.

Las células serán guardadas indefinidamente en un repositorio de células madre en la Universidad de Boston. Las células también pueden almacenarse en un repositorio central o banco.

Si está de acuerdo, sus tejidos, células o cualquier línea de células iPS o sus derivados podrían ser usados en el futuro para estudios relacionados y no relacionados, como los siguientes:

- Inyección o trasplante de células madre o sus derivados a animales para fines de investigación. Sus muestras podrían ser usadas en estudios que involucran manipulación genética, pero jamás serán usadas para clonar o reproducir a un ser humano completo.
- Pruebas genéticas y composición del ADN. Los genes pueden ser analizados o manipulados para estudiar su función normal y desarrollo. El ADN de

algunas células madre o sus derivados podría ser alterado.

- Otros usos que implican investigación o desarrollo de productos comerciales para el diagnóstico, prevención o tratamiento de diversas enfermedades.
- Las muestras obtenidas de usted en este estudio (células sanguíneas, células iPS o sus derivados) pueden ser utilizadas en el desarrollo de uno o más productos terapéuticos o de diagnóstico que podrían ser patentadas y autorizadas por los investigadores involucrados en la investigación o en el desarrollo de estos productos. No hay planes para proporcionar compensación económica si esto ocurriera.

¿Cómo puedo saber los resultados de este estudio?

La principal manera en que los resultados de este estudio son reportados es a través de publicaciones científicas y con presentaciones en reuniones científicas. En nuestros boletines informativos y en nuestro sitio web del estudio, a veces también describimos los hallazgos resumidos.

También informaremos los resultados de mediciones rutinarias de investigación a usted o a su proveedor de atención médica en el momento del examen o después de su visita. Estos pueden incluir, por ejemplo, la presión arterial y el colesterol.

En algunos casos, si determinamos que es apropiado, podemos informarlo a usted o a su proveedor de atención médica los hallazgos de investigación que se relacionen con usted si nos da su permiso para ello. Esta información, si se da a conocer, podría tomar mucho tiempo después de su visita por una serie de razones: por ejemplo, podría llevar años de trabajo para analizar la información y llegar a resultados de investigación, quizás utilizando métodos científicos que han sido desarrollados solo recientemente.

Nuestra investigación genética podría generar resultados que sean relevantes para usted y, posiblemente, su familia; tales como información sobre una variante genética en particular que lo pudiera poner en riesgo de una afección de salud grave. Por el momento, pensamos que la mayoría de los hallazgos de investigación genética no tienen gran importancia médica para las personas, pero el campo de la genética está cambiando rápidamente.

Actualmente no tenemos planes concretos de contactarlo a usted o a su proveedor de atención médica sobre los resultados de las diferentes investigaciones genéticas o no genéticas, excepto por las mediciones de pruebas rutinarias de la investigación. En general, no nos podemos comprometer a proporcionarle otros resultados del estudio. En cuanto a determinar si compartimos información adicional de la investigación con usted, tendremos en cuenta una serie de consideraciones, según cada caso en particular. Estos pueden incluir si los hallazgos se basaron en pruebas que son clínicamente aceptables, precisas y fiables, si los resultados revelan un riesgo significativo de una afección de salud grave, si existe en el momento pertinente un tratamiento reconocido o la intervención de prevención u otras acciones disponibles que tienen el potencial para cambiar el curso clínico de la condición de salud, si informar o no informar los resultados pudiera aumentar el riesgo de daño a usted, y otros factores relevantes que quizá no seamos capaces de predecir en este momento. En los casos en que se le informen los hallazgos de la investigación genética, un investigador del estudio y un asesor genético se comunicarán con usted para confirmar su interés continuo en conocer los resultados de la investigación genética. Si confirma su interés, el personal del estudio le

informará sobre los resultados de la investigación y le recomendará los siguientes pasos por seguir, como obtener pruebas clínicas de confirmación y hablar con su proveedor de atención médica personal.

Las mediciones y resultados de una investigación científica no equivalen a los resultados de pruebas clínicas. Como tal, nuestro examen de investigación no se realiza necesariamente por personas calificadas con formación clínica, y muchas partes de la examinación no cumplen con las normas requeridas para pruebas clínicas certificadas. Por esta razón, nuestras pruebas de investigación no son confiables para hacer diagnósticos, tratamientos ni decisiones para planes de salud. No brindamos atención médica, no damos consejos médicos, ni pruebas genéticas, ni brindamos asesoramiento. Si usted o su proveedor de atención médica decide hacer pruebas adicionales de seguimiento o los tratamientos necesarios, usted (o un tercero, como una aseguradora médica o Medicare) será responsable por esos costos.

¿Cómo se comparten mis muestras y mi información con otros investigadores?

Las muestras e información serán guardadas indefinidamente. Si está de acuerdo, sus datos y sangre donada, células de sangre, células iPS o sus derivados, orina y otros especímenes pueden ser compartidos con otros investigadores, incluyendo otras entidades académicas con o sin fines de lucro, como hospitales, universidades, bancos de almacenamiento de células/tejidos y repositorios, bases de datos y repositorios de datos y empresas (ya sea con fines relacionados o no con estudios de investigación). Los bancos de almacenamiento de células/tejidos y repositorios, los bancos de datos y los repositorios de datos incluyen, entre otros, los repositorios de los NIH dbGaP y BioLINCC. Los investigadores internos y externos pueden solicitar datos y materiales para la investigación. Los repositorios tienen procedimientos operativos estándar para proteger su confidencialidad. Ninguna muestra o información será etiquetada con su nombre o ningún otro identificador personal. Solo con códigos.

La información de las grabaciones de audio codificadas será analizada por colaboradores calificados dentro y fuera del BUMC. Su nombre y otros identificadores personales directos no se compartirán con estas entidades.

Usted tiene el derecho de negarse a permitir que sus datos y muestras sean usados o compartidos para futuras investigaciones. Marque la casilla correspondiente en la lista de abajo.

Si usted da su permiso para que sus datos y muestras biológicas sean utilizados o compartidos para futuras investigaciones, usted podrá retirar su autorización en cualquier momento comunicándose con los investigadores del FHS. Sin embargo, si sus datos o muestras ya han sido compartidos con otros investigadores, no podremos instruirles para que dejen de usarlos o destruirlos al igual que con los productos hechos de estas muestras. Sus datos y muestras no incluirán su nombre ni otros identificadores directos.

¿Qué riesgos puedo esperar?

Los riesgos generales y los riesgos individuales relacionados con las nuevas actividades se mencionaron anteriormente.

La participación en la investigación genética podría tener un impacto negativo para usted, su familia y sus seres queridos. Los estudios genéticos podrían producir resultados en la investigación que se relacionen con riesgos a una afección de salud grave u otra información

genética que podríamos considerar apropiado informarle a usted y a su proveedor de atención médica, si es que lo desea (véase abajo). Esto podría presentarle algunas decisiones difíciles respecto a la información disponible y correr el riesgo de saber sobre enfermedades que usted y sus miembros familiares pudieran enfrentar. Saber los resultados de una investigación genética podría ocasionar ansiedad e influir en decisiones relacionadas con el matrimonio, la planificación familiar y otros temas. Existe una pequeña posibilidad de riesgo de que su información genética se utilice en su contra. Por ejemplo, si los hallazgos de la investigación genética sugieren un problema de salud grave, eso podría usarse para dificultarle la tarea de conseguir o mantener un trabajo o un seguro. Tanto las leyes estatales de Massachusetts como las leyes federales, en particular, la *Genetic Information Nondiscrimination Act* [Ley de No Discriminación por Información Genética] (GINA), en general, prohíben que las compañías de seguros médicos, los planes médicos grupales y la mayoría de los empleadores lo discriminen en función de su información genética. Estas leyes, generalmente, lo protegerán de las siguientes maneras:

1. Las compañías de seguros médicos y los planes médicos grupales no pueden solicitar la información genética que obtendremos de esta investigación.
2. Las compañías de seguros médicos y los planes médicos grupales no pueden usar su información genética para tomar decisiones sobre su elegibilidad o primas.
3. Los empleadores de Massachusetts con 6 o más empleados (o 15 o más empleados en otros estados, según la GINA) no pueden usar su información genética que obtendremos de esta investigación para tomar la decisión de contratarlo, ascenderlo o despedirlo o para establecer los términos de su empleo.

Tenga en cuenta que ni la ley de Massachusetts ni la GINA lo protegen contra la discriminación genética por parte de compañías que venden seguros de vida, seguros por discapacidad o seguros de atención a largo plazo. Por lo tanto, las compañías de seguros de vida, de discapacidad y de atención a largo plazo pueden preguntarle legalmente si se ha sometido a pruebas genéticas y negarle la cobertura si usted se niega a responderles.

¿Qué tan protegida está mi información?

Almacenaremos su información de formas que consideremos seguras. Etiquetaremos sus muestras e información con un código y mantendremos las claves de los códigos en una base de datos protegida con contraseña. Solo al personal autorizado se le da la contraseña. Usaremos otros medios seguros en nuestras instalaciones y en nuestra tecnología y sistemas de información para proteger su privacidad y su información.

No vendemos, rentamos ni arrendamos su información de contacto.

Su nombre y otros identificadores personales directos no se usarán cuando la información de este estudio es publicada o presentada en reuniones científicas, ni cuando sus muestras o información se comparten con otros investigadores, ni cuando las guardamos en repositorios y bancos de muestras y datos.

Sin embargo, no garantizamos la privacidad total. Nosotros podemos dar acceso a su información para realizar el estudio y para asegurarnos de que hacemos el estudio, según las normas establecidas por la ética, el derecho y los grupos de calidad. La información puede ponerse a disposición de los investigadores que forman parte de este estudio, pero también de la Junta de Revisión Institucional que dirige esta investigación, de empleados y organizaciones que necesitan la información para hacer su trabajo en la realización y supervisión del estudio, personas o grupos que nos contratan para trabajar para nosotros (como empresas de almacenamiento de datos de muestras biológicas, compañías de seguros y abogados) y

organismos federales y estatales, según lo exija la ley o si están implicados en la investigación o supervisión de nuestro estudio. En la mayoría de los casos, cualquier información que se da es identificada con códigos y no con su nombre u otros identificadores personales directos. Una vez que se da información a terceros, no podemos prometer que se mantendrá en privado. Tenga en cuenta que su información personal puede ponerse a disposición si es requerida por la ley (como, por ejemplo, para evitar posibles lesiones a usted o a otros).

Este estudio está cubierto por un certificado de confidencialidad (*Certificate of Confidentiality*, CoC) de los Institutos Nacionales de Salud. Todos los estudios financiados por los Institutos Nacionales de Salud que involucran información identificable o muestras biológicas están cubiertos por un CoC. El CoC determina cómo podemos compartir información de investigación o muestras biológicas. Debido a que tenemos un CoC, no podemos entregar información de investigación o muestras biológicas que puedan identificarlo a ninguna persona que no participe en la investigación, excepto como se describe a continuación. Aunque una persona intentara obtener su información o muestras biológicas para un procedimiento legal, no podemos dársela. El CoC no le impide compartir su propia información de investigación.

Si usted acepta participar en el estudio y firmar este formulario, compartiremos información y muestras biológicas que puedan revelar su identidad con los siguientes grupos de personas:

- Personas que realizan la investigación o ayudan a supervisar la investigación, incluso el control de seguridad.
- Personas de agencias federales y estatales que auditan o revisan la investigación, según lo exige la ley. Dichas agencias pueden incluir las siguientes: el Departamento de Salud y Servicios Sociales de EE. UU., la Administración de Alimentos y Medicamentos, los Institutos Nacionales de Salud y el Departamento de Salud Pública de Massachusetts.
- Los investigadores que obtendrán sus datos y muestras biológicas, según detallamos en la sección "¿Qué sucederá en este estudio de investigación?". Se espera que estas personas protejan su información y muestras biológicas de la misma manera en la que las protegemos nosotros.

- Cualquier persona para la que usted nos haya dado permiso por separado para compartir su información.

Debe saber que estamos obligados a informar sobre abuso o negligencia infantil, maltrato a personas mayores, enfermedades de notificación específicas o daños a otras personas.

Compartiremos los datos de la investigación una vez que hayamos eliminado cualquier cosa que consideremos que podría revelar su identidad. De todas maneras, podría haber una pequeña posibilidad de que alguien pueda averiguar que la información es acerca de usted. Dicha divulgación incluye lo siguiente:

- La publicación de los resultados en revistas o libros médicos.
- La incorporación de los resultados a una base de datos del Gobierno federal.
- El uso de los datos de la investigación en estudios futuros, realizados por nosotros o por otros científicos.
- El uso de las muestras biológicas en estudios futuros, realizados por nosotros o por otros científicos.

Las muestras que se obtengan de usted en este estudio se analizarán para averiguar información sobre su composición genética. Es posible que su información genética y de salud,

sin su nombre ni ningún otro dato que pudiera identificarlo fácilmente, se incluya en una base de datos administrada por los Institutos Nacionales de la Salud (NIH). Esto podría incluir la información completa de su genoma. Otros investigadores pueden solicitarles a los NIH su información de la base de datos. Debe saber que es posible que su información genética podría utilizarse para identificarlos a usted o a su familia, aunque creemos que no es demasiado probable que esto suceda. Una vez que su información se entregue a la base de datos de los NIH, puede solicitar que los NIH dejen de compartirla, pero no podrá recuperar información que ya fue entregada.

Patentes de descubrimientos

Algún día, la investigación de este estudio resultará en nuevas pruebas para diagnosticar o predecir enfermedades. También puede llevar al desarrollo de nuevas formas de prevenir o tratar enfermedades. Como es el caso de todas las investigaciones financiadas por el Gobierno federal, los investigadores y sus empleadores tienen permitido, por la Ley Federal de Patentes de Descubrimientos, beneficiarse financieramente. Ni usted ni sus herederos se beneficiarán financieramente.

¿Cuáles son los posibles beneficios de mi participación en este estudio?

A usted no se le pagará por participar en el estudio ni obtendrá beneficios médicos como resultado de su participación. Sin embargo, esperamos que este estudio nos ayude a comprender mejor qué es lo que causa enfermedades del corazón y otras enfermedades y afecciones, así como las mejores maneras de prevenir y tratar estas enfermedades.

¿Cuáles son los costos por participar en el estudio?

Los costos que pudiera incurrir el día de su participación incluyen, entre otros, costos de transporte (gasolina, peajes, etc.) y el no poder trabajar el tiempo que esté aquí.

Usted no recibirá ningún pago por participar en este estudio.

El Estudio del Corazón de Framingham no hará arreglos especiales de compensación o pago por su participación en este estudio. Si piensa que ha sufrido una lesión por participar en este estudio, comuníqueselo de inmediato al investigador. La Universidad de Boston y los patrocinadores del estudio, no ofrecen un programa de compensación debido al costo por la atención médica que pudiera recibir si sufriera lesiones, discapacidad, dolor, malestar u otros gastos, como pérdida de salario. Si sufriera lesiones aquí y si su seguro médico no cubriera su atención médica, no le compensaremos por el gasto de la atención médica que reciba. Esto no lo hace renunciar a ninguno de sus derechos legales.

¿Cuánto tiempo estaré en el estudio?

El Estudio del Corazón de Framingham es un estudio a largo plazo.

La participación en este estudio depende solo de usted. Puede optar por participar o por no participar. Si ahora decide participar, puede cambiar de opinión y dejar de hacerlo más adelante.

Le haremos saber si encontramos información nueva que pudiera hacerlo cambiar de parecer respecto a su participación en este estudio.

El investigador puede decidir interrumpir su participación sin su autorización debido a que este considera que su continuidad en el estudio podría ser perjudicial para usted o el patrocinador puede suspender el estudio.

Lea las siguientes afirmaciones y marque la casilla apropiada abajo:

1) Estoy de acuerdo en participar en el examen del FHS, que incluye la recolección de datos, muestras de sangre, orina y varias pruebas de investigación y mediciones. Estoy de acuerdo en que se usen mis datos, muestras y materiales de investigación para los estudios de factores que contribuyen a enfermedades del corazón, los vasos sanguíneos, los pulmones y la sangre, accidentes cerebrovasculares, pérdida de memoria, cáncer y otras enfermedades y afecciones de salud.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 0*)

2) Estoy de acuerdo en permitir que mis datos, sangre, ADN y otro material genético, células iPS y sus derivados, muestras de orina y otros especímenes, sean utilizados en la investigación genética de los factores que contribuyen a enfermedades del corazón, los vasos sanguíneos, los pulmones y la sangre, accidentes cerebrovasculares, pérdida de memoria, cáncer y otras enfermedades y condiciones de salud.

   | _| SÍ | _| NO (*Para uso interno: código de oficina* 3)

3) Estoy de acuerdo en permitir que investigadores de empresas comerciales tengan acceso a mis datos, sangre, ADN y otro material genético, células iPS y sus derivados, muestras de orina y otros especímenes para investigación. Entiendo que mis datos y muestras se compartirán sin mi nombre o identificadores personales directos.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 4*)

4) Estoy de acuerdo en permitir que el FHS divulgue los resultados de los exámenes y las pruebas de investigación no-genéticas conmigo, mi médico, clínica, hospital u otro proveedor de atención médica.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 30*)

5) Estoy de acuerdo en permitir que el FHS me dé, y con mi permiso también a mi médico, clínica, hospital u otro proveedor de atención médica, información relacionada con la investigación genética referente a mí.

   | _| SÍ | _| NO (*Para uso interno: código de oficina 31*)

Sujeto:_____
Nombre en letra de imprenta del sujeto

Al firmar este formulario de consentimiento, usted indica lo siguiente:

- Que ha leído este formulario (o se lo han leído).
- Que sus preguntas se han respondido a su entera satisfacción.
- Que usted acepta participar voluntariamente en este estudio de investigación.
- Que usted permite el uso y la divulgación de información que pueda identificarlo, según lo explicado, incluso su información de salud.

Para ser completado por el sujeto si firma personalmente

_____ _____
Firma del sujeto Fecha

Para ser completado por el representante legalmente autorizado (Legally Authorized Representative, LAR) si el sujeto no firma personalmente
Doy mi consentimiento en nombre del sujeto.

_____ _____
Nombre en letra de imprenta del representante legalmente autorizado (LAR) Relación con el sujeto

_____ _____
Firma del representante legalmente autorizado Fecha

Investigador:_____
Nombre en letra de imprenta de la persona a cargo del análisis del consentimiento

Para ser completado por el investigador si el sujeto firma personalmente
He explicado personalmente la investigación al sujeto mencionado anteriormente y he respondido todas sus preguntas. Considero que el sujeto comprende lo que implica el estudio y acepta libremente participar.

_____ _____
Firma de la persona a cargo del análisis del consentimiento Fecha

Para ser completado por el investigador si el sujeto no firma personalmente
He explicado personalmente la investigación al representante legalmente autorizado del sujeto mencionado anteriormente y he respondido todas sus preguntas. Considero que el representante legalmente autorizado del sujeto comprende lo que implica el estudio y acepta libremente que el sujeto participe.

Considero que el sujeto mencionado anteriormente (marque una opción):
☐ Es capaz de comprender lo que implica el estudio y acepta libremente participar.
☐ No es capaz de comprender lo que implica el estudio.

_____ _____
Firma de la persona a cargo del análisis del consentimiento Fecha

Estudio del Corazón de Framingham,

examen 10 de Offspring, examen 5 de Omni 1

APÉNDICE DEL FORMULARIO DE CONSENTIMIENTO DE INVESTIGACIÓN

Información básica

Título del proyecto: Evaluación multidimensional de la salud cerebral como marcador de riesgo de demencia y resiliencia

Número de la IRB: H-40757

Patrocinador: Instituto Nacional sobre el Envejecimiento (National Institute on Aging, NIA), Institutos Nacionales de Salud (National Institutes of Health, NIH)

Investigador principal: Sudha Seshadri, MD [redacted]

Tómese el tiempo para revisar esta información detenidamente. Debería hablar con los investigadores sobre el estudio y hacerles todas las preguntas que tenga. Quizá también desee hablar con otras personas (por ejemplo, sus amigos, familiares o un médico) sobre su participación en este estudio. Si decide participar en el estudio, se le pedirá que firme este formulario. Antes de firmarlo, asegúrese de comprender de qué se trata el estudio, incluidos los riesgos y los posibles beneficios para usted.

Participación voluntaria: usted no tiene que participar si no lo desea. También puede retirarse del estudio en cualquier momento. Si se retira antes de su finalización, no se le aplicará ninguna sanción ni perderá los beneficios a los que tenía derecho.

El investigador principal (IP) del Estudio de Salud Cerebral es la Dra. Sudha Seshadri, profesora de Neurología en el Centro de Ciencias de la Salud de la Universidad de Texas, San Antonio, y también profesora adjunta de Neurología en la Facultad de Medicina de la Universidad de Boston. El director del programa que supervisa esta iniciativa en el centro del Estudio del Corazón de Framingham es el [redacted]

[redacted]

Descripción general del Estudio de Salud del Cerebro

Estamos interesados en encontrar otra forma distinta a la evaluación de las pruebas cognitivas para definir la salud del cerebro. Le pediremos que participe en una serie de pruebas motoras que capturarán la salud del cerebro, que incluyen pruebas de visión, audición y función motora. Se le realizará una prueba de ojos (sin dilatación); pruebas de audición (usando un iPad y auriculares) y pruebas de la función motora (que incluye la evaluación de la velocidad de la marcha en una alfombra electrónica, la evaluación durante la caminata normal y mientras se realiza una tarea mental, como contar).

El Estudio de Salud del Cerebro que está dentro del Estudio del Corazón de Framingham, examen 10 de Offspring, examen 5 de Omni 1, se realiza en colaboración con el Centro de Ciencias de la Salud de la Universidad de Texas en San Antonio.

Todos los procedimientos detallados a continuación se realizarán únicamente con fines de investigación.

A. Prueba de visión:

Angiografía por tomografía de coherencia óptica (*Optical Coherence Tomography Angiography*, OCTA):

Este examen se realizará sin dilatar las pupilas. Se le pedirá que apoye el mentón y la frente en un soporte adherido a la máquina de la OCT. Se le pedirá que fije los ojos en un objetivo durante unos segundos mientras una cámara escanea y toma imágenes de la retina, la parte posterior del ojo. También mide el flujo sanguíneo del ojo. Es una medición para nada invasiva, aprobada por la Administración de Alimentos y Medicamentos *(Food and Drug Administration*, FDA) de los EE. UU. como método rápido para evaluar la densidad capilar retiniana.

B. Prueba motora

En la ***prueba de marcha***, se le pedirá que camine sobre una estera (que parece una alfombra o tapete normal) que tiene sensores de presión debajo. Una computadora y un software conectados al tapete capturarán los diferentes aspectos de la caminata, incluida la velocidad, la longitud del paso, el ancho del paso, etc. Se le pedirá que camine a su ritmo habitual, ritmo rápido y mientras realiza tareas cognitivas, como hacer una cuenta regresiva.

C. Prueba de audición

Utilizando un sistema portátil basado en una tableta y auriculares, presentaremos al **oído** un **tono puro** midiendo la intensidad más baja en decibelios (dB) a la que este **tono** se percibe en el 50 % del tiempo. Esta medida se llama **umbral**.

Riesgos de la participación en esta investigación

Riesgos de información relacionados con el estudio

Se asignará un código numérico a sus datos. Sus muestras o datos no se guardarán con su nombre, ni número de expediente médico ni con ninguna otra información que pudiera identificarlo fácilmente. La clave que vincula su información de identificación con el código se almacenará de forma segura en un archivo separado y no se compartirá con ningún investigador que no forme parte de nuestro equipo de estudio.

El principal riesgo de permitirnos utilizar sus datos para la investigación es una posible pérdida de la privacidad. Si bien este riesgo es grave, es poco probable que ocurra, porque tomamos varias medidas para proteger su información. Protegemos su privacidad mediante la codificación de sus datos y eliminando los identificadores personales. Los resultados de la investigación obtenidos en este estudio no se incluirán en su expediente médico, a menos que nos comuniquemos con usted por un hallazgo de gran importancia médica. No creemos que haya más riesgos para su privacidad al compartir sus datos con otros investigadores; sin embargo, no podemos predecir cómo se utilizarán estos datos en el futuro.

BMC and BU Medical Campus IRB
IRB NUMBER: H-32132
IRB APPROVAL DATE: 07/21/2021

Riesgos de los procedimientos del estudio

Existe también un riesgo mínimo de caída durante la prueba de la marcha, pero tomaremos las mismas precauciones descritas anteriormente para evitar caídas, caminando detrás suyo y a su lado, y ayudándolo si es necesario.

Para obtener más información sobre los riesgos y los efectos secundarios, consulte a uno de los investigadores o al personal del estudio. Le informaremos sobre cualquier nuevo hallazgo significativo obtenido durante el transcurso de esta investigación que pueda estar relacionado con su voluntad de seguir participando.

¿Qué pasa si ocurre una lesión relacionada con la investigación?

Los investigadores han tomado las medidas necesarias para minimizar los riesgos conocidos o esperados, y no esperamos que se produzcan lesiones de estos estudios. Aun así, podría experimentar problemas o efectos secundarios, incluso aunque los investigadores sean cautelosos para evitarlos. En caso de una lesión relacionada con la investigación o si experimenta una reacción adversa, comuníquese de inmediato con el personal del estudio. Consulte la sección “Información de contacto” para obtener los números de teléfono e información adicional. También es posible que deba avisarles a sus médicos habituales.

Si sufre una lesión o enfermedad por participar en este estudio de investigación, se le brindará atención médica. Esta atención se le podría cobrar a usted o a su seguro. Dependiendo de las circunstancias, se le podría brindar sin costo alguno para usted. No ofrecemos un programa de compensación debido al costo por la atención médica que pudiera recibir por lesiones relacionadas con la investigación. El personal del estudio puede proporcionarle más información.

Al firmar este formulario, usted no está renunciando a su derecho de buscar una compensación adicional si resultara perjudicado como resultado de participar en este estudio.

Información sobre cómo este estudio utilizará su información médica protegida (*Protected Health Information*, PHI)

La información que obtengamos sobre usted en este estudio se manejará de manera confidencial, de acuerdo con lo previsto por la ley. Si publicamos los resultados del estudio en una revista o libro científico, no lo identificaremos. La Junta de Revisión Institucional y otros grupos que tienen la responsabilidad de supervisar la investigación podrían querer ver los registros del estudio que lo identifican como sujeto de este estudio.

Las políticas de investigación exigen que su información privada esté protegida, y esto es especialmente válido para su información médica. Sin embargo, la ley a veces permite o exige que otros vean su información. La información proporcionada a continuación describe cómo se protegerá su privacidad y confidencialidad de sus registros de investigación en este estudio.

¿Qué es la información médica protegida (PHI)?

La información médica protegida (*Protected Health Information*, PHI) es la información sobre la salud de una persona que incluye información que permitiría determinar quién es la persona. Conforme a la ley, usted tiene derecho a decidir quién puede ver su información médica protegida. Si opta por participar en este estudio de investigación, dará su autorización para ver y utilizar su información médica del estudio a los investigadores y al personal del estudio de investigación (las personas que realizan el estudio). Para llevar a cabo esta investigación, la

información médica que podremos ver y usar sobre usted, será la siguiente:

- Sus antecedentes médicos y análisis de sangre.
- Los resultados de las pruebas de evaluación de ojos, oídos y marcha.
- La información de entrevistas o cuestionarios.
- La información demográfica, como su edad, sexo.

Obtendremos esta información de los datos recopilados hoy y a lo largo de los años en el Estudio del Corazón de Framingham.

¿Cómo se protegerá su PHI?
Con el fin de proteger su privacidad, el personal del estudio utilizará códigos numéricos para identificar su información médica en lugar de su nombre. Las iniciales y los números se utilizarán en las fotocopias de los registros del estudio y en otros materiales del estudio que contengan información médica que se envían a las instituciones mencionadas anteriormente para su revisión o prueba. Si los resultados de este estudio se publican en revistas o en reuniones médicas, no se le identificará.

Parte de su PHI puede fotocopiarse y enviarse a una sede central o puede transmitirse de manera electrónica, como por correo electrónico, fax u otro medio seguro de transmisión. Los grupos que reciben su información médica podrían no estar obligados a mantenerla confidencial. Podrían transmitir la información a otros grupos o personas que no se han mencionado en este documento.

¿Cómo se compartirá su PHI con otros investigadores?
Debido a que es una investigación, no podremos mantener su PHI completamente confidencial. Podemos compartir su información médica con personas y grupos involucrados en la realización y supervisión de este estudio de investigación, entre ellos, los mencionados a continuación:

- Los siguientes colaboradores de otras instituciones que participan en el estudio: el Centro de Ciencias de la Salud de la Universidad de Texas en San Antonio, la Facultad de Medicina de la Universidad de Boston, la Enfermería de Ojos y Oídos de Massachusetts y la Universidad del Sur de California.
- Los miembros del equipo de investigación local.
- La Junta de Revisión Institucional y la Oficina de Cumplimiento del Centro de Ciencias de la Salud de la Universidad de Texas en San Antonio, y otros grupos que supervisan cómo se llevan a cabo los estudios de investigación.
- Las oficinas de investigación en el Centro de Ciencias de la Salud de la Universidad de Texas en San Antonio.

Si decide participar en este estudio, dará su autorización para que los grupos mencionados anteriormente recopilen, usen y compartan su información médica con fines de investigación. Si elige no autorizar a que estos grupos recopilen, usen y compartan su información médica, como se explicó anteriormente, no podrá participar en este estudio de investigación.

¿Está obligado a autorizar el uso de su información médica?
Usted no está obligado a autorizar a que los investigadores y otros grupos vean y compartan su información médica. Si elige no autorizarlos, no se aplicará ninguna sanción, pero no se le permitirá participar en la parte del Estudio de Salud del Cerebro del Estudio del Corazón de Framingham.

Después de inscribirse en este estudio, puede solicitar, en cualquier momento, a los

investigadores que dejen de usar su información médica. Sin embargo, lo deberá hacer por escrito y enviar su carta a ***Vasan Ramachandran, investigador principal, Framingham Heart Study, 73 Mt Wayte Ave, Suite 2, Framingham, MA 01702.*** Si les dice a los investigadores que dejen de usar su información médica, finalizará su participación en esta parte del Estudio del Corazón de Framingham y el personal del estudio dejará de recopilar nueva información médica de usted y acerca de usted para este estudio. Sin embargo, el personal del estudio seguirá utilizando la información médica recopilada hasta el momento en el que reciban su carta en la que les solicita que dejen de hacerlo.

¿Puede solicitar ver la PHI que se recopila sobre usted para este estudio?
Las normas federales establecen que puede ver la información médica que recopilamos sobre usted y que usamos en este estudio. Comuníquese con el personal del estudio si necesita revisar su PHI recopilada para este estudio. Si solicita información de la investigación que no está en su expediente médico, es posible que no se la proporcionemos, pero daremos una explicación de por qué no podemos hacerlo. Puede usar la información de contacto que se encuentra en la primera página de este formulario para averiguar cómo obtener su información médica.

¿Cuánto tiempo se usará su PHI?
Al firmar este formulario, usted está de acuerdo en autorizarnos a usar y a divulgar su información médica para los fines del estudio hasta el final de este estudio. En este momento, no tenemos una fecha de finalización específica y continuaremos usando sus datos hasta que dejen de tener valor científico.

Información de contacto

Si tiene preguntas ahora, no dude en consultarnos. Si tiene preguntas adicionales más adelante o desea informar un problema o una queja que puedan estar relacionados con este estudio, comuníquese con las personas o instituciones a continuación:

[redacted]

El comité del Centro de Ciencias de la Salud de la Universidad de Texas que revisa la investigación en seres humanos (Junta de Revisión Institucional, IRB) responderá cualquier pregunta sobre sus derechos como sujeto de investigación y tomará cualquier inquietud, comentario o queja que desee presentar. [redacted]

Sección de firma de autorización y consentimiento para la investigación

Si usted acepta participar en esta investigación y acepta el uso de su información médica protegida en esta investigación, firme esta sección. Se le entregará una copia firmada de este formulario para que la guarde. Al firmar este formulario, usted no renuncia a ninguno de sus derechos legales.

FIRME ESTE FORMULARIO SOLO SI LAS SIGUIENTES AFIRMACIONES SON VERDADERAS

- Usted ha leído la información anterior.
- Sus preguntas se han respondido a su entera satisfacción.

Sección de firmas de los adultos

- Usted ha decidido de forma voluntaria participar en este estudio de investigación.
- Usted autoriza la recopilación, uso y divulgación de su información médica protegida, como se describe en este formulario.

Nombre en letra de imprenta del sujeto	Firma del sujeto	Fecha

Sección de firma del representante

- Usted otorga, de forma voluntaria, su consentimiento para que otra persona participe en este estudio, porque considera que esta persona querría participar si pudiera tomar la decisión y considera que es lo mejor para esta persona.
- Usted autoriza la recopilación, el uso y el intercambio de la información médica protegida de otra persona, como se describe en este formulario.

Nombre en letra de imprenta del sujeto	Firma del **Sujeto**, que indica el consentimiento *(Si no puede firmar, la persona que obtiene el consentimiento deberá poner sus iniciales aquí)*	Fecha

Nombre en letra de imprenta del representante legalmente autorizado (*Legally Authorized Representative*, LAR)	Firma del representante legalmente autorizado (LAR)	Fecha

Investigador

Nombre en letra de imprenta de la persona que obtiene el consentimiento y la autorización	Firma de la persona que obtiene el consentimiento y la autorización	Fecha

Informed Consent

A waiver of Informed Consent has been approved for the Offspring and Omni 1 Cohorts However, as there are new components in the current exam cycle, the waiver of Informed Consent will not be administered unless the participant is cognitively impaired and a LAR is not available. Participants will be re-examined in the FHS Research Center. Health updates, research, and use of data and materials will continue by prior consents. A Medical Authorization form and the research proxy form will also be offered to the participants. New consent forms will emphasize descriptions of new research activities. Identified LARs may be asked to sign the informed consent in cases of cognitive impairment.

Cognitive capacity is assessed in interviews by trained admitting staff. If impairment is observed, the LAR is given the same information as the participant, and advised of the components of the exam that have been determined to be greater than minimal risk. A research proxy, a LAR appointed prior to the onset of cognitive impairment, may give consent for components of the exam that are greater than minimal risk. If a research proxy has not been appointed, the next of kin may sign as a LAR, but only for those research activities that are of no greater than minimal risk. If the participant does not have a LAR, only the exam components to which the participant has previously given informed consent will be administered.

Dissent of our participants or their LAR will always be honored regardless of cognitive capacity.

Informed consent is administered to each participant by a trained interviewer prior to the collection of any research study data. The "consent form" is a two-part document. The first part is a narrative description of the study goals, the content of the exam, the risks and benefits of participating, the study's confidentiality policy, each person's right to withdraw from the study, and compensation in the unlikely event that participation results in the need for medical care. The second part is the participant's authorization page, which the participant signs. The informed consent document complies with the National Heart, Lung, and Blood Institute guidelines and is approved by Boston University Medical Center's IRB.

I. Overview

Informed consent is the first data collection form administered during the FHS exam. Only updated versions of the informed consent form, approved by the BUMC IRB will be used. All study subjects will be provided with:

(1) a description of what data collection procedures will be followed and what is involved in each case;

(2) the benefits and risks of participating in a research study which includes genetic analysis;

(3) a description of what procedures are in place to protect their confidentiality;

(4) information on their right to withdraw from the study, to not participate in a procedure or to decline to answer a question(s) without penalty;

(5) an opportunity to document their preference for the use and disposition of their study data and genetic materials; and

(6) a record of and a mechanism for contacting the project director/principal investigator and the study coordinator.

II. Administration

The FHS staff person obtaining Informed Consent must provide ample time for the participant to read the consent and answer any questions the participant may have. Each interviewer should be trained to administer the consent form and to use the developed procedure for presenting the form to the participant. The Training Guide for Administrators follows below.

During the consent process the consenter must "…minimize the possibility of coercion or undue influence…" (46.116 Code of Federal Regulations). One does this by allowing the participant to make their decision to participate on their own, without time constraints during the consent process. Participants must be given "…sufficient opportunity to consider whether or not to participate…", and if the participant refuses the exam their wishes must be honored (46.116 Code of Federal Regulations).

Once the participant has agreed to participate in the current exam cycle, their consent must be documented. This is done by using "…a written consent form approved by the IRB and [the consent must be] signed and dated by the subject…" (50.27 Code of Federal Regulations). Note: Be sure to use the current version of the approved consent, if you have any question of what consent should be used please contact the FHS IRB Administrator.

Special attention is paid to the following details during the consent process.

Consent Check Boxes

The introduction of the check boxes gives participants options for participation and a clear understanding of each statement that requires a yes or no answer. Participant responses are documented for data collection and any negative responses are reported to the appropriate manager for follow up.

Photocopying Consents

A photocopy of the participants signed consent must be given to the participant. According to the Code of Federal Regulation 21CFR 50.27 *Documentation of Informed Consent* "(a)…informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject…at the time of the consent. A copy shall be given to the person signing the form."

For offsite visits, the signed consent will be copied and mailed to the participant after the visit.

Training Guide for Administrators of the FHS Informed Consent

Suggested language:

The Framingham Heart Study is required to give you detailed information about the exam so you can decide whether or not you want to participate. We call this process INFORMED consent.

Introduction to the Checkboxes

This section of the consent form asks for your permission for non-genetic and genetic studies. It allows you choices in your participation in FHS research studies and allows you choices in regards to having test results sent to your personal physician or other healthcare provider.

Checkbox 1 asks your permission for the examination today and all of the testing.

For Example: The questionnaires, the MD visit, lung functioning tests, blood samples and other non-invasive testing of your heart and blood vessels. This allows FHS researchers to study non-genetic factors contributing to heart and blood vessel diseases, as well as other diseases and health conditions.

Checkboxes 2-3 have to do with the blood samples we are obtaining today and participation in genetic studies. Your name is not linked to any of the genetic studies.

Checkbox 2 allows you to agree to participate in genetic studies of factors contributing to heart and blood vessel disease, lung and blood vessel disease, stroke and memory loss.

These health conditions are the core research mission of the Framingham Study.

Checkbox 3 allows you to provide permission to the FHS to allow researchers from private companies to have access to you DNA and genetic data.

Researchers from private companies may be interested in studying Framingham data to develop diagnostic tests or new medications that may benefit many people.

Checkbox 4 allow the Framingham Heart Study to release findings from your examination today such as blood pressure readings, blood work results and results of your lung function tests to your physician or other healthcare provider.

Checkbox 5 allow the Framingham Heart Study to notify you in the future if researchers identify a genetic condition that may have potentially important health consequences and beneficial treatments exist for the condition.

You would only be notified if the risk for the disease is significant, the disease has important health implications and there are proven therapeutic or preventative interventions available. None of the current research meets these criteria however; it is possible in the future that genetic information with important health consequences might be discovered.

National Heart, Lung, and Blood Institute

BOSTON UNIVERSITY

Authorization to Release Health Information

Individual Current/Last Residence Contact Info, If applicable	*Name of Individual*		*Date of Birth*
	Street		*Apt. or Suite No.*
	City	*State*	*Zip*
	Home phone	*Mobile*	
	Email		
Provider	I authorize _____ To release my health care information to:		
Recipient: **Framingham Heart Study**	Framingham Heart Study, a project of the National Heart, Lung, and Blood Institute of the NIH and Boston University Framingham Heart Study 73 Mt. Wayte Ave Suite 2 Framingham Ma 01702 [redacted]		
Purpose(s)	Research purpose related to the Framingham Heart Study		
Records Requested	FOR DATES _____ to _____		
	Face Sheet Discharge Summary ER Reports Admission Notes Progress Notes CT Scans MRI/MRAs Mammograms	Lab Reports Consults Cardiac Catheterization Reports Exercise Tolerance Tests Echocardiograms Nursing Home Notes Operative Reports	Pathology Reports Arteriography Ultrasound X-Rays EKGs EEGs Notes Near Time of Death Other
Form of Records (Check selection)	I request that the health information be sent by: **Fax ☐ Mail ☐ Secure Email ☐**		

I understand that:

1. This authorization is voluntary and I have the right to refuse to sign it.
2. I may revoke this authorization at any time by providing a written notice of revocation; however such revocation will not affect any action taken in reliance on this authorization before receipt of my written revocation.
3. Refusal to sign or revocation may affect my participation in particular research studies if the information is needed for the research purposes.
4. This authorization will expire in ____ years. Health information that has been released may be kept, used and shared for research purposes after the expiration date. A new authorization may be required for the release of health information that is requested after the expiration date.
5. The medical information obtained pursuant to this authorization may be shared with others in accordance with applicable research consents and state and federal laws.
6. The medical information obtained will be used for research purposes; studying the causes of coronary disease, stroke, cancer, other major diseases, morbidity and mortality.

For individuals: I certify that I am legally competent to authorize this release; I have carefully read and I understand this Authorization; and I have had any questions explained to my satisfaction. I expressly and voluntarily authorize the release of the information as indicated above.

Signature _____ Date _____

For Next of Kin/Legally Authorized Representatives: I certify that I am the individual's Next of Kin or other legally authorized representative; I have the power and authority to authorize this release; I have carefully read and I understand this Authorization; and I have had any questions explained to my satisfaction. I expressly and voluntarily authorize the release of the information as indicated above.

Signature of Next of Kin/Legally Authorized Representative _____ Date _____

Relationship to Individual _____

Next of Kin/ Legally Authorized Representative	*Name of Next of Kin/Legally Authorized Representative*		
Address	*Street*	*Apt. or Suite No.*	
	City	*State*	*Zip*
Contact Info If applicable	*Home Phone*	*Mobile*	
	Email		

The Framingham Heart Study

Research Proxy Form

One of the most important goals of the Framingham Heart Study (FHS) is to keep track of any major changes in your health through the end of the study. This information is important for answering scientific questions about heart disease and other health conditions. You are the best source of information regarding your health, but there may come a time when you are no longer able to provide details of your health. We are asking you to name a person who can answer questions about your health and give consent for FHS research if you cannot. This person will be considered your "proxy" for the Framingham Heart Study.

What is a proxy?
A proxy is someone who can "stand in" for you and tell us about your health when you cannot because of a physical or mental illness.

Why is a proxy needed?
For many years you have been providing important information about your health to FHS. This information should be updated, even if you are unable to provide it.

What does a proxy do?
We will ask your proxy to give consent for your research participation and answer questions about your health, just like the questions you have been asked at each exam cycle on your medical history update.

Whom should I name as my proxy?
You should select someone who knows you well enough to provide health information about you. For example, your proxy can be your power of attorney, your legal health care proxy, or your legal next-of-kin (including your spouse, son, daughter, brother, sister, etc.).

Am I allowed to change my proxy?
Yes, you may change your proxy at any time by calling FHS, [redacted] or by indicating your wishes at your FHS examination.

Will you give my proxy information about me?
No, all of your information is strictly confidential and will not be provided to your proxy.

What would you like me to do now?
Using the attached form please indicate whom you have chosen to be your proxy. Please indicate his/her name, contact information, relationship to you, and then sign the form.

You will be given a copy of this form for your own records and one to give to your proxy. This material should be kept by your proxy so he/she understands your wishes as a participant in the Framingham Heart Study.

[redacted] call Maureen Valentino [redacted] 43.

Thank you for your continued dedication to the Framingham Heart Study!

Framingham Heart Study Research Proxy

FHS ID: ___ - _____ Participant Name:_____
First MI Last

I, living at _____ appoint the following person(s) to make decisions about my participation in the Framingham Heart Study ("Research Proxy"):

Research Proxy:	Alternate: If Research Proxy cannot serve or continue to serve, I name this person (Optional):
Name: _____	Name:_____
Relationship to Participant: _____	Relationship to Participant_____
Address: _____	Address:_____
_____	_____
_____	_____
(City) (State) (ZIP)	(City) (State) (ZIP)
Telephone:_____ _____	Telephone:_____ _____
(Home) (Work)	(Home) (Work)
_____	_____
(Other)	(Other)

Effective Date and Termination

This durable power of attorney shall take effect when signed by me and shall not be affected by lapse in time or by my subsequent disability or incapacity which makes me unable to make decisions about participation in research.

Powers of Research Proxy

My Research Proxy shall have the authority to make all research participation decisions for me, including decisions about whether or not to enroll me or continue my participation in a research study [both minimal and greater than minimal risk research procedures as determined by the federal regulations and in consultation with the IRB]. My Research Proxy is to have the same authority to make research participation decisions as I would have. S/he has the authority to provide medical information and to consent for testing and examinations,. S/he further has the power to authorize the provision of records related to payment, treatment or services to me or on my behalf from any hospital, physician, or medical source to the Framingham Heart Study.

I, the undersigned Principal, by signing my name to this declare that I understand its contents and that I sign it willingly.

_____Principal Date:_____

[*Complete the following if the Principal is physically incapable of signing*:]

I hereby sign the name of the Principal at the Principal's direction and in the presence of the Principal and two witnesses.

Name of Signer: _____
Date: _____
Address of Signer: _____
_____

Witness Signature/Date Witness Signature/Date

_____ _____

The Framingham Heart Study (FHS) is a long term community health study which began in 1948 to identify factors associated with the development of atherosclerotic and hypertensive cardiovascular disease. The FHS Laboratory is responsible for sample collection, processing, testing, result reporting and data management activities. In addition, the lab maintains an extensive sample repository.

Sample Collection and Processing

Sample collection and processing criteria are determined for each study group prior to the exam cycle. Labels used for specimen collection vacutainers are generated. A set is placed in the participant's exam folder, which is assembled before the exam date. Generation of these labels is linked to the Roster of the Framingham Heart Study; therefore the integrity of the ID number is assured. Each study group has a label procedure for each exam cycle. Vials are labeled the morning before specimen collection begins.

At the time of the blood draw the phlebotomist review the consent and note any negative responses. Negative responses might change the types of tubes drawn. A test request form is filled out for all participants, it is a CLIA regulation. The test request label includes the FHS ID number, name, sex, exam number and exam date. The phlebotomist fills in the time of draw. All blood test the participant will get results for is listed on the form. The phlebotomist then asks the participant his or her name, and confirms the name and ID number on the labels. Participants are asked to fast for 12 hours. If a participant is diabetic, ask what type of medication they are on and if they needed to eat after the blood draw. Communicate this info with the research center staff. Participants are drawn in a supine position. Blood draws are done using a butterfly needle, either 21 or 23 gauge. The tourniquet can stay on for 1 minute or less. If more time is required, it is documented. Participants are also asked to provide a urine specimen. This specimen is

collected in a cup labeled with their name, ID number and the number void for the day.

Samples for long-term storage are stored in screw cap microsample tubes with an O-ring cap. Samples that will be assayed fresh are transferred into 5 ml polystyrene test tubes with push in stoppers. Microsample tubes are organized in racks according to the aliquotting diagrams that are established for each study group. Prior to centrifugation, allow the first EDTA tube drawn to rock for 5 minutes before transferring 1 ml of whole blood for HbA1c testing into a 5ml barcode labelled tube. Allow the A1c aliquot to mix on the rocker until ready to run on the Cobas c311. EDTA tubes and citrates can be spun immediately. Red top serum vacutainers must sit at room temperature for a minimum of 30 minutes to allow for complete clotting. The time draw is written on the label after phlebotomy. To balance the centrifuge, arrange the Vacutainers in the centrifuge carriers so that the carriers opposite each other are mirror images. Use Vacutainers filled with water if necessary. Lock the centrifuge safety shields into place and then close the cover. All tubes are centrifuged for 22 minutes at 4C at 2500g.

Sample Aliquotting

EDTA==Remove EDTA tubes from centrifuge. Measure the volume in each EDTA tube and transcribe onto Mastersheet. Carefully remove the stopper from EDTA tube #1. Using a transfer pipette and being careful not to disturb the white or red cell layers, aspirate the plasma. Do not lower the tip of the transfer pipette to within 5mm of the buffy coat layer. Transfer plasma to a labeled 13mL tube. Aliquot approximately 1mL of the plasma into a labeled 5mL tube for fresh analyses. Use the Repeater Stream automatic pipette to aliquot plasma from the 13mL tube into cryovials. Transfer the plasma from the remaining EDTA tubes, one tube at a time, aliquotting the plasma as you proceed. After transferring the plasma, collect the buffy coat layer from the EDTA tubes using the transfer pipette. Transfer the buffy coat

from tube #1 to the appropriate BC aliquot tube. Repeat the procedure for additional tubes. Using a clean transfer pipette, aspirate approximately 1 mL of red cells from the EDTA tube #1. Transfer the red cells into aliquot tube RBC1. Repeat the procedure for any additional tubes.

SERUM==Carefully remove the stopper from serum tube. Using a plastic transfer pipette and being careful not to disturb the cells, aspirate the serum. Do not lower the tip of the transfer pipette to within 5 mm of the clot. Transfer serum to a labeled 13mL tube. Aliquot approximately 1mL of the serum into a labeled 5mL tube for fresh analyses. Use the Repeater Stream automatic pipette to aliquot serum from the 13mL tube into cryovials.

URINE==Using a plastic transfer pipette, transfer the urine into each of the aliquot tubes using the above diagram as a reference for tube size and sample volume. Transfer approximately 3 mL of urine into aliquot tubes. Cap the aliquot tubes. Discard extra urine. Note urine void number. Dispose of the vacutainers in biohazardous waste container. Place rack into the –80C freezer. All samples should be placed into the freezer within 90 minutes of draw. When time permits, file each aliquot into the appropriate spot in the storage boxes. Samples should be frozen for at least one hour before filing.

Testing

The tubes designated for routine analyses are transported to the chemistry testing area. The routine run include cholesterol, triglycerides, HDL and glucose (run on plasma), albumin, ALT, AST, creatinine and Total Protein (run on serum) and HbA1c on whole blood. Samples are analyzed on Roche cobas c311 system. All assays are calibrated at intervals recommended by Roche. Assays are calibrated on initial start-up, if there are concerns about a specific test and if calibration verification fails. Calibration records are maintained for each assay. Calibration

date, calibration factor(s), reagent lot number and calibrator lot number are recorded.

Commercial control materials are used with every set of participant samples. Observed values are compared to target ranges. This range is the target mean plus or minus two standard deviations. Means and standard deviations are calculated for each new lot of control materials based on data from an overlap period, during which the old lot and the new lot are run simultaneously. All chemistry assays are run with control materials at two or three different levels. Control materials are handled identically to participant samples. Controls are run at the beginning of every set. All assays are calibrated at intervals recommended by Roche.

Program the Cobas to perform the required assay test. Results are transcribed onto the daily lab worksheet. Technician initials the completed run. After testing is complete all results are checked for QC, repeats and call levels. Control values from every set are recorded on QC datasheets, which are maintained for all assays. Also recorded on the QC sheets are reagent lot changes, calibrations, instrument maintenance and any comments about the run. In addition, the FHS Lab uses a software program, Unity Realtime, to record and generate statistics and Levy-Jennings charts for QC data. QC statistics for all assays are summarized weekly and reviewed monthly by the laboratory manager and laboratory supervisor. Some chemistry assays which are reported to participants and their HCP's are measured in duplicate. The average of the two values is reported. We have established limits for acceptable differences between replicate values. If a pair of duplicates does not fall within the acceptable range, the participant assay is repeated. For serum creatinine and albumin, the replicates must be within 0.1 mg/dl. For HbA1c, the replicates must be within 0.3%.

Blinded repeat measurements of laboratory assays are made for quality control purposes. A new phantom is collected for every 20 participants. A phantom participant is created using extra samples drawn from several Heart Study participants. Phantom Log Sheets are used to create a record, matching the

phantom ID to the ID's of the source participants. The bar-coded label for the phantom ID is affixed to the top of the form. As samples are collected for the phantom, bar-coded ID labels identifying the source participants are added to the log sheet. When complete, a phantom sample set will be identical to the sample set of a standard participant for that study (including serum, plasma, red cells and urine samples).

Alert results should be call into the participant's doctor. Urgent results are brought to the attention of a Center nurse practitioner as well. All data required to generate Lab Reports are loaded into a data management software through RedCap by the Lab Manager. Lab Reports are generated weekly from data management software. A SAS report is generated that is compared with the original runs. All corrections are highlighted, the correct value is written and is inserted into RedCap. At this time, lab reports can be generated. They are compared with each other as well as the original runs. If an alert/urgent action was taken, a letter notifying the participant will also be generated and included in the final report. Two copies of the lab report and any letters are sent upstairs for filing. A record stating the results were verified as well as HDL ratio and EGFR is checked and initialed.

Hematology: Place holder

Temperature Monitoring and other Maintenance

The following temperatures are recorded daily: room temperatures, refrigerators, freezers and refrigerated centrifuges. Settings and alarms for all freezers are also checked and recorded. The Framingham Study currently maintains twenty-two ultra low temperature freezers (-80 C) and two standard freezers (-20 C). All freezers are monitored by Stanley Security and Rees Centron Monitoring System. In addition twenty-one ultra low temperature freezers are maintained off site at Fisher Bioservices in Franklin MA.

Emergency back-up power is supplied by a Kohler 40KW generator. This generator unit includes a 150 gallon tank for diesel fuel. This would supply 48 hours of back-up power. The Kohler generator is exercised once a week. The fuel level of the generator is checked monthly.

Maintenance procedures for the cobas c311 instrument are fully described in the manufacturer's operator's manuals. There is a schedule of routine, daily, weekly, monthly and quarterly maintenance. All maintenance is recorded on Maintenance Log Sheets, including scheduled maintenance, as well as trouble shooting maintenance and service calls.

Framingham Heart Study
Offspring Exam 10/ Omni Exam 5
Laboratory Protocol
Draft

Blood samples are collected from participants in a supine position, after a 10-hour fast.
The following tubes are drawn:

3 x 10 mL EDTA blood collection tubes
2 x 10 mL Serum blood collection tubes
4 x 4.5 mL Citrate blood collection tubes
2 x 1.6 mL Hirudin blood collection tubes

Total volume of blood draw is 71.2 mL (4.8 T or 2.4 ounces).

EDTA

1. EDTA whole blood is used for measurement of HbA1c, and a CBC with a 3-part WBC differential; performed daily in the FHS laboratory.
2. EDTA plasma is used for measurement of cholesterol, HDL-cholesterol, triglycerides and glucose; performed daily in the FHS laboratory.
3. EDTA plasma, red cells and buffy coat are saved in several aliquots for future testing; stored at -80^{o}C.

Serum

1. Serum is used for measurement of creatinine, albumin, ALT and AST; performed daily in the FHS laboratory.
2. Serum is saved in several aliquots for future testing; stored at -80^{o}C.

Citrate

1. Citrate whole blood and plasma is used for platelet function testing; performed daily in the FHS laboratory.
2. Citrate plasma is saved in several aliquots for future testing; stored at -80^{o}C.

Hirudin

Hirudin whole blood is used for platelet function testing; performed daily in the FHS laboratory.

Urine (Random, spot urine)

Urine is saved in several aliquots for future testing; stored at -80^{o}C.

If a participant faints or you suspect they may:

- Withdraw the needle immediately.
- Talk to the participant to divert their attention from the procedure and to keep them alert.
- Keep the participant supine and have them breathe deeply.
- Apply a cold compress or washcloth to the forehead and back of the neck.
- If needed ask for assistance from research center staff.
- When the participant begins to feel better offer crackers and or something to drink.
- Once the participant recovers they should remain in the area under supervision for at least 15 minutes or until they have fully recovered.
- Have participant evaluated by Research Center Nurse Practitioner.
- Nurse Practitioner will document the incident as an adverse event on the Exit Interview Form in RedCAP. A copy is given to the Senior Recruiter and one copy is placed in participant chart. In addition a Medical Encounter form is also filled out an placed in the first page of participant chart.

FHS Gen2/Omni1 Exam 10/5 Platelet Study

PI: Andrew Johnson (NHLBI)

Background notes: Very similar protocols were proposed and run in the last Framingham Heart Study exam. Thus, we are experienced with running these assays and instruments, their quality control and analysis.

Total burden to all protocols listed here:
1) Bleeding history questionnaire (<=5 min, self-administered)
2) 3x4.5mL sodium citrate blood tubes (Roche); 2x1.6mL hirudin blood tube (Sarstedt)

Staff training: Several members of our staff have years of experience with these instruments and protocols. Any new staff will be trained by experienced staff through shadowing, and use of these detailed written protocols. Periodic volunteer QC blood draws may also be used, particularly in the time period before the actual exam starts. There are no clinically reported results from these protocols so certification is not required.

Equipment and calibration schedule
(note in this setting all instruments are RUO):

1) Bio/Data PAP-8E light transmission aggregometer
   daily QC checks built-in; yearly LTA-Check test run and certified
2) Multiplate (Roche) impedance aggregometer
   daily QC checks built-in; monthly Liquid controls are run
3) T-TAS instrument
   there is routine maintenance/changing pump oil, etc but no specific calibration; there are built in pump and camera sensors that will trigger errors if there are major issues
4) Optimul absorbance assay/plate reader/freeze drier
   no specific maintenance; QC as below
5) microVISC viscometer
   the microVISC has built-in sensors if flow or other technical issues are experienced; QC as below
6) BD Biosciences Accuri C6 flow cytometer

under service contract; but no specific calibration; instrument has daily setup and shutdown checks and cleaning (which will trigger errors if there are major problems)

7) Centrifuge, heat block, plate washer and other basic equipment
   no specific maintenance schedule but all equipment new within the last several years; plate washer will detect if things are out of alignment

Quality control and certifications:

No specific certifications are required as we are not reporting clinical results. The PAP-8E does get re-certified annually.

We conduct detailed QC analyses as we have done in the last exam. This includes examination of month-to-month and/or batch-to-batch variation; and utilization of blinded, phantom blood-draw tubes periodically (about 3.5% of samples) to assess assay reproducibility and whether there are any systematic changes that would require troubleshooting.

Data collection:

1) We keep a paper log of lab processing – for example time of blood draw, time of each assay step, time of centrifuge, volume of PRP, and any other notes on particular samples or assays. These paper logs are entered into a computer log to help with potential analysis and trouble-shooting later if needed
2) RedCap – bleeding history questionnaire
3) Instrument data

Medically actionable results: as with the last exam these assays are RUO and there is no likely reportable finding.

Detailed Exam Procedures:

1) Bleeding history questionnaire (attached separately). Uses skip-logic. In our past experience, ~82% of participants answer No to all questions and will navigate quickly through the questionnaire without ever seeing an expanded question.
2) Lab preparation and measurement protocols. Detailed procedures follow for all steps on the following pages:
   a. Plasma preparation (p.3)
   b. PAP-8E LTA (p.4-9)

c. Multiplate (p.9-10)
d. T-TAS (p.10-17)
e. Viscometry (plasma/wb) (P.17-21)
f. Flow cytometry (P.21-23)
g. Making Optimul plates (P.23-28)
h. Optimul plate assay (P.29-30)
i. Preservation of samples for later use (P.30)

Plasma Preparation

Machine footprint (centrifuge): 24" (D) x 17"(W) x 14"(H)

Time (all samples): ~1 hour (most of this is not hands on time freeing personnel to work on other things; much of the extra time is due to spinning with no brake)

Timing is also dependent on sequence and clustering of blood draws. If blood draws are spread out over several hours, it is often best to have 2 rounds of spinning for PRP and PPP (early and later samples) so that assays can begin on the early samples

1.) Check and record the blood draw time in the data log.
2.) There should be 3 sodium citrate tubes (blue caps) for a normal draw.
    a. If there are fewer tubes, make a note in the data log.
    b. If there are 5 tubes, this means we have a "Phantom" for QC purposes. Record the phantom number in the phantom log.
3.) Let the plasma sit, undisturbed, on the benchtop for 15 minutes.
4.) Load the tubes in the centrifuge and spin on Program one to isolate platelet rich plasma (PRP)
    a. 10 min at 200 RCF.
    b. Acceleration setting is 3 and deceleration setting is 5.
5.) Pipette the PRP fraction of each sample into a 15mL conical tube.
6.) Recap the draw tube and return to the centrifuge.
7.) Spin tubes on Program 2 to isolate platelet poor plasma (PPP).

a. 15 min at 1,500 RCF.
b. Acceleration setting is 3 and deceleration setting is 5 (same as before)

8.) Remove the tubes from the centrifuge. You may now begin plasma testing.

PAP-8e LTA Operation

Machine footprint: 22"L x 14" W x 5" H

Time (per sample): ~15 minutes

Time (startup/walk away/shutdown/cleaning): 20 minutes for startup, agonist preparation,

releasates storage of all samples at end of day

Preparation:

1. Open the LTA software and click "Continue" to start the test block heating.
2. Pull out the test platform.
3. Remove pre-made agonists from storage and allow to warm to room temp.
    a. Collagen and Epinephrine are stored at 4C
    b. Ristocetin, TRAP-6 amide, and Arachidonic Acid are stored at -20C
4. Prepare fresh 9.5µM, 18.2 µM, and 57.1 µM ADP solutions.
5. Once the machine has reached 37C, log in and proceed to sample testing.

Sample Testing:

Note: this monitor is a touch screen. You may use touch or the mouse at any point, according to your preference. Moisture in the touch screen may cause difficulties and should be wiped immediately.

1. Click "Routine Aggregation."
2. A menu will pop up. Select "Multiple Tests" from the dropdown menu and click ok.

3. On the next screen, click “Run Sample.”
4. On the next screen, scan the appropriate sample ID into the first two fields in ROW 1.
5. Click “Fill Down,” then click in the second field in ROW 8. All of the first and second fields should auto-populate with the sample ID scanned into ROW 1.
6. Click “Template.” A new screen will appear. In the dropdown menu, select the appropriate test template (ours is “fhsNEW”), then click “Load.” You will be returned to the previous screen.
7. The third column should have auto-populated with the following tests:
    a. Channel 1 – Arachidonic Acid (AA)
    b. Channel 2 – Collagen (Coll)
    c. Channel 3 – 9.5µM ADP
    d. Channel 4 – 18.2µM ADP
    e. Channel 5 – 57.1µM ADP
    f. Channel 6 – Epinephrine (Epi)
    g. Channel 7 – AggRecetin (Risto)
    h. Channel 8 – TRAP-6
8. Place a cuvette in each of the 8 slots at the back of the test platform, and one cuvette in one of the stirred incubation wells (for the blank). Make sure each cuvette is free of debris and scratches.
9. Place a magnetic stir bar in each cuvette, including the blank.
10. Pipette 25µL Normal Saline into the blank tube.
11. Check that the PPP and PRP tubes you are going to use match the sample ID on the screen.
12. Pipette 225µL of PPP into the blank tube.
13. Make sure the PRP tube is securely capped, and invert once (gently) to mix.
14. Pipette 225µL of PRP into each of the 8 test cuvettes.
15. Click next. You will be brought to the test screen.
16. Move the blank into Channel 1, checking for stir bar and correct volume. Press cuvette down all the way.

17. Move the 8 test cuvettes to the stirred incubation wells (middle row on the test platform). Check for stir bar and correct volume in each cuvette.
18. Start the incubation timer by clicking any of the buttons at the top of the screen that display "0:00." This will begin a 2-minute countdown.
19. Close the channel covers, and click "Blank" for Channel 1. The button will gray-out and may blink for 1-10 seconds. This is normal.
20. When the letters turn black and the word "Start" replaces "Blank," you may open the channel cover. Opening the cover before blanking is complete may result in inaccurate blanking.
21. Move the blank cuvette to Channel 2 and repeat blanking procedure. Continue until all channels have been blanked.
22. When blanking is complete, move the test cuvettes forward into the test channels. Double check for stir bar and correct volume in each cuvette.
23. Firmly but gently, press down on each cuvette to ensure proper alignment. Mis-seated cuvettes will result in inaccurate data.
24. Close the channel covers.
25. When the timer beeps, begin agonist injection.
26. Pipette 25µL of the appropriate agonist (agonist order in Step 7) into each well. To proceed:
    a. Aspirate 25µL of agonist.
    b. Press "Start" on the computer screen for the desired agonist test channel. The button below will turn green and read "Inject."
    c. Set pipette tip in the correct slot, making sure the ridge of the pipette tip is flush with the cover surface, and dispense agonist.
    d. Press "Inject" on the computer screen.
    e. Discard tip, and repeat this step until all 8 agonists have been injected.
27. Click the "Test Block" tab (top right) to view data graph.
28. The test takes 6 min. from the "Start" time for each agonist. The timer will beep when each channel finishes.
29. When each test finishes, check the "Test Block" tab and review the aggregation plots.
    a. Click the "Status" button

b. If sample passes, click "Accept."
c. If sample fails, click "Reject." Record reason for rejection in the Data Log. Common reasons for rejection include:
    i. Incorrect or suspected incorrect agonist injected.
    ii. Cuvette was not pressed down.
    iii. No stir bar.
    iv. Unusual sample profile. Repeat to confirm.
d. To enter a comment for any sample (optional) to so click "CMMNT" and enter it.
e. When you are done, click "Done."

30. Discard used cuvettes in the biohazard waste.
31. Click "Menu," and exit to the Main screen
32. Proceed to next Participant Sample and repeat Sample Testing procedure until complete.

LTA -saving sample releasates

Part 1: making the diclofenac-heparin solution

Heparin is a biologically active species. Different lots of lyophilized heparin may have different activity even if the weight is the same (e.i. 10mg of lot A might not be as active as 10mg of lot B). As such, calculations are done based on heparin activity rather than weight. The "U/mL" unit designates activity.

Heparin is sold both by weight as lyophilized powder or in solution at a designated activity. Either is acceptable for this assay. The Framingham Heart Study currently uses heparin from lyophilized powder

1.) Make a 500 U/mL heparin stock solution.
    a. If using heparin purchased in solution, dilute to correct concentration in DI water.
    b. If using heparin in powder form, do the following:

i. Determine the activity for the lot. If this information is not included in the product packaging, it can usually be found on the manufacturer's website by going to the product page and downloading the Certificate of Analysis for the desired lot. The lot's activity should be listed there (sometimes it is labelled "anti-xa"). The unit should be "U/mg" unless otherwise stated.

ii. Calculate the volume of water necessary to reach the desired concentration as follows:

[(Activity in U/mg) x (weight of vial in mg)] ÷ 500U/mL = X

where X is the volume (mL) of DI water used to resuspend the powder.

iii. Resuspend in appropriate amount of water.

c. Store solution at 4°C.

2.) Make the 1 mM Diclofenac Sodium + 10U/mL Heparin solution. The following recipe is enough for about 90 samples.

a. To a 50mL conical tube, add 95.4mg diclofenac sodium salt.
b. Add 3mL DMSO.
c. Vortex vigorously until the diclofenac is completely dissolved.
d. Add 24.6mL PBS.
    i. Do not add PBS until the diclofenac is completely dissolved, otherwise it will fall out of solution over time.
e. Add 600µL of 500 U/mL Heparin stock.
f. Invert to mix.
g. Store solution at 4°C. Solution is stable for at least one month.

Part 2: Saving the releasate

1.) Run PAP-8e LTA test (see LTA protocol above)
2.) Immediately upon test completion, add 25µL of the 1 mM Diclofenac Sodium + 10U/mL Heparin solution to each test cuvette, including the PPP blank.
3.) Use a transfer pipette to move the plasma from each cuvette to a separate well in a covered 96-well plate (must be rated to withstand a 10min spin at 1,000xg).

4.) Once all the LTA tests for the day are completed and plasma is removed to the covered 96-well plate, place plate in the centrifuge and spin for 10 minutes at 1,000xg to pellet platelets.
5.) Transfer the supernatant to a fresh covered 96-well plate, taking care not to carry over the pellet (pellet should be fairly tight and difficult to disrupt). This step is best accomplished with a p300 multichannel pipette.
6.) Seal the plate with a foil 96-well plate sealing sticker. Be sure to press seal firmly between wells to prevent spillover.
7.) Store the plate at -80°C until use.

Multiplate Operation

Preparation:

1. Turn on the heat block by opening the Multiplate software.
2. Fill the Normal Saline tubes and place them in the incubation slots to warm them.
3. Remove pre-made agonists from storage and allow to warm to room temp. (Collagen stored at 4C; Risto, TRAP, and ASPI are stored at -20C)
4. Prepare fresh 98.8µM ADP.
5. Once the Multiplate machine has been at 37C for 20 minutes, run the daily electronic QC.

Sample Testing:

1. Let the Hirudin blood sit, undisturbed, for at least 30 minutes post draw time.
2. Click "Auto Pipette." Scan the bar code for the first sample into the sample id field, and click "Use ID for all tests"
3. Select a test for each channel. They should be in the following order:
    a. Channel 1 – 1_ADP
    b. Channel 2 – 2_Collagen
    c. Channel 3 – 3_Risto
    d. Channel 4 – 4_TRAP
    e. Channel 5 – 5_ASPI
4. Place a test cell in each channel, making sure that the stir bar is in the bottom of each cell.
5. Connect each sensor cable to the corresponding test cell.
6. Click Start, check that the tests are in the correct order, and then click start again.

7. Pipette 300µM normal saline into each cell, following screen instructions. The machine is programmed to dispense the correct volume of fluid at each step.
8. Invert the Hirudin whole blood tube 6 times (gently).
9. Double check that the ID on the tube matches the ID on the screen.
10. Pipette 300µM whole blood into each cell, following screen instructions.
11. Wait for the incubation period (3 min).
12. When the machine dings, add the appropriate agonist to each test cell.
    a. Channel 1 – 20µL of 98.8 µM ADP
    b. Channel 2 – 20 µL Collagen
    c. Channel 3 – 50µL Risto
    d. Channel 4 – 20µLTRAP
    e. Channel 5 – 20µL ASPI
13. Wait until the test is done (6 minutes). Check that the CC is >0.985 and the DIFF is >20. If these criteria are not met, it may be necessary to re-run the test.
14. Once complete, click "Stop Channel," select "stopped channels," and click "OK."
15. Detach the sensor cables from the test cells, then discard the used test cells in biohazard waste.
16. Proceed to next sample and repeat Sample Testing procedure until complete.

T-TAS Protocol

Machine Startup

1. Turn on the T-TAS laptop.
2. Turn on the T-TAS machine (flip power switch on the right side).
3. Wait for the machine to turn on; it will make a few mechanical noises.
4. Open the T-TAS application.
5. A small window will open titled "Select Mode." Select "AR Standard/ PL Standard" and click OK.
6. Another small window will open titled "Select USB." Select "A7OOF9ES" (should be the only option), and click OK.
7. The application will open. At the bottom of the left-hand application window, there will be a yellow box that says "Under initializing," and a small window will open saying "WARNING! Don't touch PC & device for completion of device behavior."
    a. Wait for yellow box to turn grey and acquire the heading "Measure Result Status" before proceeding, then click OK in "WARNING!" window.

8. At the top of the application window, there is a “Chip Type” dropdown menu. Select “PL chip,” then click “DECISION.”
9. From the “Shear Selection” dropdown menu, select “Mid Shear (manual rec.)”
10. Check the oil tank volume.
    a. If the oil volume is greater than 1,700ul proceed to step 11
    b. If the oil volume is less than 1,700ul, fill the tank before proceeding. To fill:
        i. Check the tubing from the mineral oil bottle to the oil tank for bubbles. If there are bubbles:
            1. Click on the “System Check & Maintenance” tab.
            2. Towards the bottom, there will be a box labelled “Select Valve.” Select the “Tank” radial button.
            3. In the “Micro Pump” box, click “Injection.” The button will gray-out.
            4. The bubbles should now move through the tubing back into the mineral oil bottle. Once all of the bubbles have been removed from the line, click the grayed-out “Injection” button to stop the oil flow.
            5. Return to the “Measure” tab, and click the “Oil Supply” button.
            6. A window will pop up asking you to confirm starting the oil supply process. Click ok.
            7. The window will now read “Now Supplying Oil!” You may click “Stop” at any time to halt the process.
            8. The filling process will automatically stop when the tank is full, and a window will appear saying “Then, prior to use, ‘system check’ it.” Click OK.
            9. Proceed to step 11.
11. Click on the “System Check & Maintenance” tab.
12. Towards the bottom, there will be a box labelled “Select Valve.” Select the “Chip” radial button.
13. In the “Micro Pump” box, click “Injection.” The button will gray-out.

14. The if there are any bubbles tank-to-chip line, they should now move through the tubing and out the nozzle.
    a. Make sure to hold the nozzle away from the machine with a Kimwipe underneath to avoid dripping oil into the machine.
    b. There will almost always be bubbles in this line at the start of the day.
15. Once all of the bubbles have been removed from the line, click the grayed-out "Injection" button to stop the oil flow.
16. Wipe any excess oil off the nozzle and insert it firmly into the white SC fitting **without** removing the fitting from its resting place.
    a. You should hold the nozzle as vertical as you can when inserting it into the fitting to avoid warping the nozzle, which could impact data quality.
17. In the "System Check" box, click start.
18. A window will appear reminding you to insert the nozzle into the SC fitting if you have not already done so. Click OK to start the check. Do not touch the nozzle or adjust any settings while the check is running.
19. The check will automatically stop once completed, and the "Result" field will display the result.
    a. If "Result: Success," proceed to step 20.
    b. If "Result: Failure," remove the nozzle from the SC fitting and check the following:
        i. Re-examine the tank-to-chip line for bubbles (most likely issue).
            1. If found, repeat bubble purge (steps 13-16)
        ii. Check the oil tank for bubbles.
            1. If found, pump a small amount of oil back into the mineral oil bottle and re-fill the tank (step 10.b.i.).
                a. This may not remove bubble, but it should move it to a neutral position.
        iii. Examine the nozzle and SC fitting for debris.
            1. If found, gently remove debris with a Kimwipe.
        iv. Check for any leaks or bad connections in the oil line.
        v. Rerun the system check until "Result: Success."

20. Once the System Check passes, remove the nozzle from the SC fitting (you may remove the fitting from its holder to do this). Return the nozzle to its holder.
21. The T-TAS machine is now ready for sample testing.

Running a sample: PL-Chip

1. Remove appropriate number of test chips from the freezer and allow them to come to temperature (about 30 minutes, 2 tests per chip).
2. When you are ready to begin, remove the chip from the package, and set the chip on the warming block. The chip should remain there for no more than ten minutes.
3. In the "System Check and Maintenance" tab, make sure that the radial button in the "Select Valve" box is set to "Chip"
4. Click on the "Measure" tab.
5. Make sure chip type is set to PL-chip and shear is set to "Mid shear (Manual rec)".
6. At the top of the screen in the "Sample Name" field, enter the test name, making sure to include the participant ID number and the operator initials.
7. Move the camera arm up by squeezing the two metal plates together and sliding the camera arm up.
8. Remove the focus chip and set it aside (skip this step if not the first test of the day).
9. Remove the plastic stickers from the channels of the PL-chip, and place the chip lengthwise, lining up the indentations on the bottom of the chip with the corresponding protrusions on the machine surface.
10. Press the chip down so that it sits firmly on the machine surface, without wiggling.
11. Lower the camera arm so that it rests on the surface of the chip.
12. At the bottom of the screen in the "Camera" box, set the camera to the chip channel you will be using by clicking "move to (left or right) path." There will be a whirring sound from the machine as the camera moves, and you will see the repositioning in the camera window on the screen.
13. Adjust the camera position to capture desired portion of the chip.
    a. Adjust left/right position by using the knob closest to the power switch on the right side if the machine.

b. Adjust up/down position by using the up/down arrow buttons on the front of the machine.

14. Adjust the focus using the knob closest to the front on the right side if the machine.
15. Check the tank -to-chip line for bubbles. If present, remove by running oil though the line.
    a. Bubbles anywhere in the oil line or test assembly impact the pressure distribution in the test system and invalidate test results. It is imperative that there be no air bubbles anywhere in the assembly for collection of accurate and valid data.
16. Remove the nozzle from its resting place and hold it away from the machine.
17. Hold a Kimwipe below the nozzle to prevent oil spillage into the machine, and press the "OIL" button on the front of the T-TAS unit.
18. Once a small droplet of oil has emerged, wipe off excess oil with the Kimwipe.
19. Gently but firmly insert the nozzle into the small end of the PL-chip reservoir. Make sure that the nozzle is snug and there are no gaps or air bubbles between the nozzle and the reservoir.
20. Place the nozzle assembly in the reservoir holder, making sure not to kink the oil line.
21. Wet pipette 320µl of Hirudin blood into the reservoir.
    a. If the blood has been sitting for longer than a few minutes, gently pipette up and down 3-4 times to mix.
    b. Hold the pipette at an angle, roughly 2/3 of the way down to the bottom of the reservoir, touching the tip to the reservoir.
    c. **Slowly** expel the blood so that it runs down to the bottom of the reservoir so that there are no bubbles between the nozzle opening and the blood surface. If there are bubbles **do not proceed**.
        i. Bubbles in the reservoir impact the pressure distribution in the reservoir. In case of bubbles:
            1. Use the eye of a darning needle to scoop out small bubbles.
            2. Use a p10 or p20 pipette to deflate larger bubbles.

3. If unable to remove bubbles, remove the blood from the reservoir, discard the reservoir, and start again.

22. Remove the assembly from the holder, holding the reservoir in one hand and an overcap in the other.
    a. This typically works best when the overcap is held in your dominant hand.
23. Hold the overcap at a slight angle to the reservoir and insert into the reservoir opening, again avoiding bubbles.
    a. Holding the overcap at an angle significantly reduces introduction of bubbles.
24. Press the overcap firmly into the reservoir so that the lip of the reservoir is flush with the lip of the overcap. Excess blood should flow into the detachable part of the overcap, preventing the introduction of bubbles inside the capped reservoir.
25. Twist the overcap while still pressing down, then gently pull the detachable portion of the overcap off while continuing to twist. The chamber holding the excess blood should come off easily.
26. Using the lip of the detached chamber, scrape off any blood that may ooze out of the reservoir/assembly opening so that the blood is flush with the opening, then discard the detached chamber.
    a. If a large amount of blood remains, use a kimwipe to wick it away.
27. Position the reservoir assembly over desired chip channel, centering it over the opening. Make sure to hold the sides of the reservoir and NOT the nozzle connection.
28. Once the assembly is lined up correctly, press the reservoir straight down in one smooth motion, firmly and without twisting, so that the reservoir is snug and flush inside the chip opening.
29. Double check that all connections are flush and there are no bubbles in the system.
30. Begin the test.
    a. Click the “Start” button in the center of the application window.
        i. A window will appear reminding you to check the oil supply volume. Click “OK.”
    b. Click the “Start Recording” button at the bottom right of the application window.

31. Blood will begin flowing through the test channel, the timer on the camera will turn red and start counting up, and pressure data will be displayed in the graph window.
    a. Accidentally centering the camera over the wrong channel will not impact flow pressure data, as long as the test channel has not been used previously.
    b. You may reposition the camera at any time during the test without interrupting pressure data collection.
32. When base kPA +10 is reached, the time will be displayed in the T10 field (usually around 3 minutes).
33. The test will continue until either of two conditions are reached:
    a. Total pressure exceeds base kPa + 60 (occlusion threshold)
        i. "Measure Result Status" field will say "Complete: Run up to Occlusion Pressure"
    b. Ten minutes has passed without the occlusion threshold being reached.
        i. "Measure Result Status" field will say "Complete: Time up to AUC Time"
34. When the test is completed, the screen will flash once, the timer will stop and turn grey, the AUC10 at the bottom of the application will display the final AUC, and the "Measure Result Status" field will say "Complete:" with a message indicating which stop condition was met.
    a. It is easy to mistake whether the test is complete since blood usually continues to flow for some time after the test is complete, so be sure to check that the final AUC is displayed and the Measure Result Status" field with displays "Complete:" message before continuing.
35. Gently remove the reservoir from the chip, and then remove the reservoir from the nozzle.
    a. It is necessary to disassemble the test setup in this order to prevent blood from leaking.
36. Discard the used reservoir and return the nozzle to its holder.
37. If both channels of the chip have been used, slide the camera arm and discard the chip. Otherwise, leave the chip in place for the next test.

38. Test data will automatically save, and you may proceed to the next test. If you are done for the day, proceed to shutdown procedure.

T-TAS shutdown: PL-chip

1. Dispense a small amount of oil from the nozzle to make sure the tip is clean by pressing the "OIL" button on the front of the T-TAS unit.
2. Using a Kimwipe, wipe the excess oil from the nozzle, and place the nozzle in its holder.
3. Return the focus chip to the test platform, making sure to line up the pins on the platform with the holes in the chip.
4. Slide the camera arm down to the lowered position.
5. Fill the oil tank, as in step 10 of the Machine Startup section.
6. Once the oil tank is filled, close the application.
7. A window will pop up with the text "Cleaning EDTA Path with H2O is recommended. Time required: 20(sec)."
    a. Click "Cancel," since the PL-chip process does not use EDTA.
8. Another window will open asking "Are you sure that the tube is free of EDTA?"
9. Click "Yes."
10. The application will close. After about 20 seconds, the camera light on the T-TAS machine will start flashing.
11. Flip the power switch to the "Off" position. At this point you may hibernate/shut down the laptop.

Plasma and Whole Blood Viscometry

Machine footprint: 13"L x 13"W x 9"H

Time (per sample): ~2 minutes

Time (startup/walk away/shutdown/cleaning): ~20 minutes incubation time; personnel are free to do other things during this time

Note: It is possible to run the viscometer using the built-in keypad on both the measurement unit and the heating unit. This protocol uses the software provided by the manufacturer at time of instrument purchase. Please refer to the machine's user manual for keypad instructions.

Note: If testing both plasma and whole blood, the manufacturer recommends running all of the plasma samples first, then running all of the whole blood samples.

1.) Turn on both the small viscometer unit and the larger heating unit.
2.) Press the temperature control "On/Off" button on the heating unit to enable heating function.
3.) In the microVISC Control software, click the "Temperature" tab and set the temperature to 37°C. Make sure to click "Set," otherwise the unit will not heat.
    a. You may also wish to adjust the "Minimum Stability" and "Stability Window Length" parameter settings, as the default is fairly restrictive for practical use
    b. It may take 10-15 minutes for the unit to reach the desired temperature.
4.) Load the sample pipette by inserting it into the test liquid (either whole blood or plasma) and slowly pulling up on the plunger.
    a. Take care not to over-fill the pipette. Doing so will extend the plunger too far back, and the pipette will not fit into the test area.
    b. Once pipette is loaded, handle only by the flange.
        i. Holding by the barrel may cause unwanted heat transfer.
        ii. Holding by the plunger may cause accidental ejection of fluid or introduction of bubbles.
5.) Check the pipette for bubbles. If bubbles are present, hold the pipette vertically with the tip facing upwards, and gently flick the side of the pipette until the bubbles rise to the top. Press the plunger just enough to push the bubbles out of the pipette.
6.) Wipe the excess liquid from the outside of the pipette with a lint-free wipe to prevent particulate from being introduced into the test chamber.
7.) Mount the pipette into the viscometer by placing the tip at the inlet port and pressing down on the flange until it clicks into position.

a. Securing the flange takes a fair amount of pressure. Keep pressing until you hear it click.

8.) Close the lid of the heating unit, and double check that the temperature setting is correct.

9.) Allow the loaded sample to reach the test temperature (37°C).
    a. Manufacturer recommends an equilibration time of 20 minutes.

10.) In the "Operate" tab, enter desired test parameters using the "Measurement Mode" dropdown menu, then entering parameters where applicable.
    a. System defaults to "Automatic." All test parameters will be determined by the machine's internal measurements.
    b. "Advanced" allows user to define several parameters. Leaving a field blank or entering "0" will result in an automatic determination for that parameter. Definable parameters include:
        i. "Rate Values" -shear rate.
        ii. "Priming Volume"- volume of sample used to prime the system before measurement begins.
        iii. "Pausing Time"- time elapsed between end of priming step and start of measurement step.
        iv. "Measurement Volume"- volume of sample used to determine viscosity measurement.
    c. "Cleaning" initiates a cleaning cycle. In most cases, this is not necessary at instrument start-up.

11.) Double check that the temperature is stable, then click "Start."
    a. Do no open the lid or touch the sample until the sample is done running.

12.) Test data is automatically saved and may be accessed via the "Data" tab.

13.) Once the measurement is complete:
    a. If you wish to do so, AND there is sufficient volume remaining in the pipette, you may run another test on the sample. To do so, adjust the test parameters (if desired) and click "Start." If you wish to repeat the run with the same parameters, simply click "Start."

i. This process may be repeated until the volume remaining in the pipette is insufficient to continue.

b. Once the final measurement is completed, open the heating unit lid and press down on the metal lever next to the pipette flange to release the pipette.

14.) Discard the used pipette. Reloading/reusing may result in inaccurate or inconsistent results.

15.) Once the used pipette has been removed, there are several choices:

a. If you are running the another of the same sample type, return to step 3.

b. If you are running another sample that is a different type but is of similar viscosity, return to step 3 WITH THE EXCEPTION that you must discard the first reading due to sample mixing that may skew results.

i. Example: If completed sample was PRP, but the next sample will be whole blood, discard the first reading on the whole blood sample.

c. If you are going to test a sample of significantly different viscosity, perform a cleaning cycle (see next step) before continuing.

i. This is not an issue for switching between whole blood and plasma.

d. If you have completed measurements for the day OR it will be more than 1 hour before the next sample is tested, proceed to the next step.

16.) Run a cleaning cycle.

a. If more samples are going to be run:

i. Fill a pipette with Aquet detergent (1%) and mount as in steps 3-6 above.

ii. Select "Cleaning" from the "Measurement Mode" tab and click "Start."

iii. Once cycle is complete, return to step 3 to run next sample

b. If sample testing is complete:

i. Dampen a lint-free wipe with Aquet detergent (1%) and wipe excess sample from around the inlet port.

ii. Dip a lint-free swab in the Aquet solution and wipe the interior walls of the sensor cartridge inlet.

iii. Fill a pipette with the Aquet solution and mount as in steps 3-6 above.

iv. Select "Cleaning" from the "Measurement Mode" tab and click "Start."

v. Once cycle is complete, leave the empty pipette in the machine until the next time the instrument is used.

17.) Once the final cleaning cycle of the day is complete, switch off both machines.

18.) Empty the waste container and clean with your lab's preferred disinfectant and biocide. (The Framingham Heart Study uses CaviCide, but any disinfectant suitable for use in a BSL2 lab is fine.)

Flow Cytometry Protocols

Whole Blood Platelet Counts

Preparation:

1. Let Hirudin blood sit undisturbed for 30 post-draw.
2. Gently invert 6 times to mix and pipette 100 µL into a separate 2mL tube
3. Prepare 1x BD FACS Lysing Buffer in DI water from the 10x stock. (2mL per sample).
4. Prepare antibody mixture as follows:

   2.5µL CD61 antibody

   10.0µL CD45 antibody

   10.0µLCD14 antibody

   277.5µL Staining Buffer

Sample Treatment:

1. Add 2mL diluted lysis buffer to the microfuge tubes containing 100µL whole Hirudin.
2. Cap the tube and vortex until mixed, 2-3 seconds.
3. Incubate tubes at room temperature for 15 minutes.
4. Spin for 5min at 500rpm at max acceleration/deceleration.
5. Pipette off and discard the supernatant.
6. Resuspend pellet in 1mL Stain Buffer.
7. Cap the tube and vortex until mixed, 2-3 seconds.
8. Incubate at room temperature for 10 minutes.
9. Spin for 5min at 500rpm at max acceleration/deceleration.
10. Pipette off and discard the supernatant.

11. Resuspend pellet by pipetting in 300µL of antibody mix. Do not vortex.
12. Transfer mixture into an appropriately labeled flow tube.
13. Samples may now be run on the flow cytometer.
    a. Slow speed
    b. Run with Limits: 10,000 events

ADP Stimulation Assay

Preparation:

1. Prepare antibody mixture as follows (this formula will make enough mix for one flow sample).

    2.5µL CD61 antibody
    2.5µL CD63 antibody
    10µL CD62 antibody
    10µL PAC-1 antibody
    25µL PBS

2. Prepare fixation buffer. You will need 1150µL stain solution per flow sample. Calculate the total volume needed and prepare it as follows:

    1 part Cytofix
    3 parts Stain Buffer

3. In separate 2mL tubes, make a 1:40 dilution of PRP and whole blood (WB) in PBS (10µL sample + 390µL PBS).
    a. Let Hirudin blood sit undisturbed for 30 post-draw, then gently invert 6 times to mix before pipetting.
    b. PRP should be pipetted out of the spun sodium citrate tubes and combined prior to this step (see PRP/PPP Preparation protocol). Invert PRP tube once to mix before pipetting,
4. Flick tubes to mix.
5. For each participant, label four 5mL round-bottom flow tubes as follows:
    a. PRP+NS
    b. PRP+ADP
    c. WB+NS

d. WB+ADP

Sample Stimulation:

1. Add 5µL of Normal Saline to each of the tubes labeled “NS.”
2. Add 5µL of 200uM ADP to each of the tubes labeled “ADP.”
3. Add 45µL of diluted and mixed PRP to each of the tubes labeled “PRP.”
4. Add 45µL of diluted and mixed whole blood to each of the tubes labeled “WB.”
5. Cap the tubes and gently swirl or tap the tubes to mix.
6. Incubate on a dry heat block at 37°C for 15 minutes.
7. Remove tubes from the heat block, and add 50µL antibody mix.
8. Return tubes to the 37°C heat block for 15 minutes.
9. Remove tubes from the heat block, and add 1150µL staining solution mix.
10. Samples may now be run on the flow cytometer.
    a. Slow speed
    b. Run with Limits: 10,000 events

Optimul plate-making protocol

Part one: Gel coating

1.) Prepare gel coating solution, using Table 1 as a guide. Select the number of plates needed, and use the masses/volumes in the corresponding column to make the gel coating solution.
    a. Make Buffer A: Monobasic NaH_2PO_4 monohydrous in DI water
    b. Make Buffer B: Dibasic Na_2HPO_4 anhydrous in DI water
    c. Combine buffers A and B, then dilute with DI water to make Buffer C.
    d. Add gelatin and Tween 20 to buffer C
    e. Stir at 500rpm for 20 minutes before use
2.) Pipette 150uL of gel coating solution into required wells. It is not necessary to gel coat wells that will not be used when adding agonist or running sample.
3.) Let plates sit, undisturbed, at room temperature for at least 4 hours.
4.) Wash plates 2x with 0.01% Triton X-100

5.) Wash plates 2x with DI water.
    a. It is recommended to use a plate washer for steps 4 and 5, however washes may be done by hand. If washing by hand, wash 3x with water to ensure complete removal of the Triton solution.
6.) Let plates air dry overnight at room temperature.
    a. Plates may be stacked to conserve space. If stacking, stagger plates to allow airflow. Additional dry time may be required.
7.) Plates should be stored covered to prevent dust/detritus from settling into the coated wells.
8.) Gel coated plates are stable for 6+ months before adding agonist.

Part two: Adding agonist

1.) Prepare required buffers
    a. 25ml of 0.1% ascorbic acid in PBS.
    b. 4ml of 0.1% ascorbic acid in DI water.
    c. 4ml of 0.1% ascorbic acid in Ethanol.
    d. 4.4ml of 0.1% ascorbic acid, 0.18% glucose, 5% human serum albumin (HSA). This should be done stepwise.
        1. Add 9mg glucose to 5ml of 0.1% ascorbic acid and invert to dissolve.
        2. Add 220mg HSA to 4.4ml of above and gently invert to dissolve, avoiding bubbles.
2.) Prepare agonist working stock solutions (Table 2, columns B & C).
    a. Exclude Arachidonic Acid. To prevent agonist oxidation, this must be the last agonist pipetted into to the test plates and must be prepared immediately before pipetting.
3.) Pipette buffers for dilution into a deep-well 96-well plate ("dilution plate").
    a. Appropriate buffer found in Table 2, column D.

b. To row A of the 96-well plate, add the volume of buffer found in Table 2, column E
c. To rows B through H of the dilution plate, add the volume of buffer found in Table 2, column G.

4.) Add the appropriate volume (Table 2, column F) of agonist working stock to row A of the dilution plate, pipetting up and down 4-5 times to mix thoroughly.
5.) Perform serial dilutions by pipetting the appropriate volume (Table 2, column H) from dilution plate row A into row B and pipetting up and down 4-5 times to mix thoroughly, and so on, stopping at row G.
    a. Do *not* add agonist to row H, as the wells in row H are used as blanks to remove background signal.
6.) Spin the dilution plate briefly (5-10 seconds using the "short" or "pulse" button on the centrifuge) to collect all solutions at the bottom of the wells.
7.) Using an electronic multichannel pipette, add 5ul of agonist to the corresponding position on the experimental plates, being careful to pipette the liquid into the bottom of the wells.
8.) Once all agonists have been pipetted, prepare the Arachidonic Acid agonist in the same manner as the rest of the agonists with the following two exceptions:
    a. The working stock is used as the top well dilution, rather than making a separate dilution.
    b. Do *not* spin the dilution plate after agonist preparation is complete. It is unnecessary for Arachidonic Acid since it is in ethanol and allows more time for agonist oxidation and ethanol evaporation.
9.) Pipette agonist as in step 7.
    a. Pipetting the diluted agonist up and down 2-3 times before pipetting into the plates. This serves 2 functions
        i. Mixes the agonist. Arachidic acid does not go into solution well in ethanol. Mixing prior to pipetting helps ensure consistency across all plates.
        ii. Prevents agonist dripping out of the pipette tips while in-process due to the low surface tension of ethanol.

10.) Gently stack the plates into stacks of 5-7 plates each and place in a -80°C freezer.
    a. Place a clean piece of aluminum foil on the freezer shelf before placing the plates inside to prevent freezer "snow" collecting on the bottom of the plate.
    b. Cover the plates with a clean piece of aluminum foil to prevent freezer "snow" falling into the wells.
11.) Freeze the plates at -80°C for 2-4 hours.
12.) About 20 minutes before removing the plates from the freezer, turn on the lyophilizer (freeze-drier) to allow it to reach -40°C or lower.
13.) Remove the plates from the freezer and stack them in the lyophilizer.
14.) Turn on the pump and close the vacuum valve on the lyophilizer. Test that a vacuum is being generated by pulling up on the lid.
15.) Lyophilize the plates for 8 hours or overnight.
16.) Release the vacuum valve, turn off the pump, and *carefully* remove the plates from the lyophilizer. At this point, the agonist can easily become dislodged from the side of the wells, causing it to jump into other wells or out of the plate entirely. To prevent this kind of damage:
    a. Only handle the plates by the sides or the end that does not have agonist.
    b. DO NOT touch the bottom of the plate.
    c. Be careful not to drop, jostle, or rattle the plates in any way.
17.) Vacuum seal each plate individually, while continuing to handle carefully.
    a. Hold the vacuum bag open as much as possible when sliding the plate inside.
    b. Try not the move the plate around once it is in position.
18.) Once all of the plates are sealed, wrap them in aluminum foil and store them at room temperature until use.
19.) Plates expire 12 weeks after being prepared. Do not use them past expiry.

Table 1

Solution	Ingredients	Unit of Measure	40 Plates	60 Plates	80 Plates	90 Plates
Buffer A	Monobasic NaH2PO4 monohydrous	mg	110.4	165.6	220.8	248.4
	DI water	mL	40	60	80	90
Buffer B	Dibasic Na_2HPO_4 anhydrous	mg	568	852	1136	1278
	DI water	mL	200	300	400	450
Buffer C	Buffer A	mL	38	57	76	85.5
	Buffer B	mL	162	243	324	364.5
	DI water	mL	200	300	400	450
Gel Coating Buffer	Buffer C	mL	400	600	800	900
	Gelatin	g*	3	4.5	6	6.75
	Tween 20	µL**	200	300	400	450
*Note that this is g, not mg.						
**Note that this is µL, not mL.						

Table 2

Column A	Column B	Column C	Column D	Column E	Column F	Column G	Column H
	Working Stock Dilution			Top Well Dilution		Subsequent Dilutions	
Agonist	Amount of Agonist	Volume & Diluent	Buffer for Plate Dilution	Buffer (µL)	Stock (µL)	Buffer (µL)	Previous (µL)
Arachadonic Acid	1 Vial	1026.4 µL EtOH	Ethanol +0.1% Ascorbic Acid	Use "Working Stock Dilution"		385.5	514.5
ADP	1 Vial	100µL DI water (need 2 vials)	PBS + 0.1% Ascorbic Acid	340	160	333.4	66.6
Collagen	1 Vial	950µL PBS + Glucose + HSA[ǂ]	PBS + Glucose + HSA + 0.1% Ascorbic Acid	476	224	375	125
Epinephrine	1 Vial	500µL H2O	PBS + 0.1% Ascorbic Acid	460	40	300	66.6
Ristocetin	15mg Vial	375µL Saline (need 2 vials)	H2O + 0.1% Ascorbic Acid	115	460	250	333.6
TRAP-6	1 Vial	150µL Saline (need 2 vials)	PBS + 0.1% Ascorbic Acid	340	160	350	155.4
U44619	Frozen Aliquot[♯]	Frozen Aliquot[♯]	PBS + 0.1% Ascorbic Acid	340	160	300	85.6
PAR4	1mg	1.469mL PBS	PBS + 0.1% Ascorbic Acid	450	300	210	525

[ǂ]HSA- Human Serum Albumin; NS- Normal Saline

[♯] U46619 agonist comes as a pre-diluted stock at 10mg/ml. Dilute 11.2µL of stock agonist in 20.8µL ethanol. Remove 30 µL to a separate tube and dilute in 968µL PBS with 0.1% ascorbic acid. Dispense into 165µL aliquots and store at -80°C until use.

Optimul 96-well plate assay.

Machine (plate reader) footprint: 18”L x 15”W x 6”H

Machine (orbital plate shaker) footprint: 7”L x 6”W x 4”H

Time: ~8 minutes/per sample (once PRP and PPP plasma isolated from centrifugation)

Preparation:

5. Turn on the Optimul plate reader. It will perform a self-check and make a series of grinding and clicking noises. This is normal.
6. Turn on the heated orbital plate shaker and set to 37C.
    a. Switch on.
    b. Press the + symbol above the word “temp” until the display reads 37C.
    c. Press start.

Sample Processing:

14. Unwrap the foil on a pre-made, agonist coated 96-well plate.
15. Examine the plate for any loose or missing agonist. Discard damaged or incomplete plates.
16. Remove the vacuum-sealed wrapping and re-inspect the plate.
17. Pour the PRP to be tested into a reagent trough.
18. Using a multichannel pipette, wet pipette 40µL of PRP into plate columns 2-8, rows A-H.
    a. Wet pipetting may also be referred to as “reverse” pipetting. This is done to prevent the addition of excessive bubbles.
19. Using a single channel pipette, wet pipette 40µL of PRP into well 1E.
20. Wet pipette 40µL of PPP into wells 1A-D, being careful not to disturb the red cell layer in the draw tubes.
21. Gently tap the plate on the counter to make sure all liquid is on the bottom of the wells.
22. Examine each well for bubbles. Scoop any bubbles out of the well with the eye of a darning needle.
23. Stir the top 2 wells of the Risto row, since they have a tendency not to dissolve completely otherwise.
24. Read the plate at 595nm on a plate reader.
    a. Because this protocol requires a starting and ending plate read, it is ideal to create a protocol using the plate reader software to handle the reads
25. Once the read is complete, place the plate on the orbital shaker and shake for at 37C for 5 minutes at 1,200 RPM
26. When the incubation is complete, remove the plate and check it again for bubbles and debris.
    a. You may wish hold the plate at a steep angle and tap the side to help aggregates fall to one side of the well so that it does not interfere with scanning.
27. Return the plate to the scanning tray, and re-read at 595nm.
28. Export the file to an Excel file.
29. Run the Excel macro, which is designed to format the data for easy analysis, and save the resulting sheet as a .csv (comma delimited) file.

30. Make sure to save the read file from the plate reader before closing.
31. Repeat the "Sample processing" procedure for each participant.

Unused/leftover sample handling

PRP- saving for future RNA studies

Time: 10 minute spin, then ~2 minutes /per sample. Personnel free to work on other things during spin.

1.) Pipette unused sample PRP into a 2mL screwcap freezer tube. Split between multiple tubes as necessary. Be sure to label tubes.
2.) Spin samples for 10 minutes at 1,000 RCF.
3.) Remove and discard supernatant.
4.) In a fume hood, resuspend pellet in 1mL TRIzol reagent. Pipette carefully to completely resuspend.
    a. TRIzol is a highly toxic carcinogen and can penetrate nitrile gloves. Handle with care and remove contaminated gloves immediately.
5.) If you have multiple tubes from the same sample, there are 2 options regarding how sample is saved.
    a. Pipette 1mL TRIzol into each tube and resuspend pellets separately for storage separately.
    b. Pipette 1mL TRIzol into one tube and resuspend. Once pellet is resuspended, remove liquid into the next tube and resuspend pellet in the same TRIzol as the first. Be sure to remove all liquid from the first tube.
6.) Make sure the screwcap is closed tightly, and store samples at -80°C until needed.

PPP- saving for future ELISA studies

Time: ~1 minute /per sample

1.) Pipette unused sample PPP into two 2mL screwcap freezer tube, split evenly between each tube. Be sure to label tubes.
2.) Make sure the screwcap is closed tightly, and store samples at -80°C until needed.

Standing Height Measurement Protocol

1. Participant should be barefoot or wearing thin socks. Ask participant to stand erect with his/her back to vertical mounted stadiometer.

2. Heels should be together and against the vertical ruler, both feet flat on the floor, with weight distributed evenly across both feet. Check to make sure both feet are back against the wall.

3. Participant faces straight ahead with his/her head positioned in the Frankfort horizontal plane (see next page). The lower margin of the bony orbit (the socket containing the eye) should be on the same horizontal plane as the most forward point in the supratragal notch (the notch just above the anterior cartilaginous projections of the external ear).

4. Ask participant to let arms hang freely by the sides of the trunk, palms facing the thighs. Ask participant to inhale deeply and maintain a fully erect position.

5. Bring the level down snugly (but not tightly) on top of participant's head.

6. Record measurement to the **nearest 1/4 inch, rounding down.**

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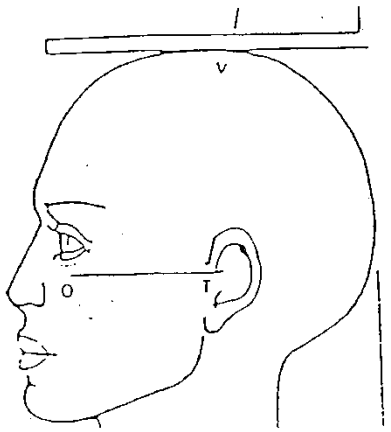
Standing Height Measurement

FRANFORT PLANE FOR MEASURING BODY HEIGHT



ORBITALE: Lower margin of eye socket
TRAGION: Notch above tragus of ear or at upper margin of zygomatic bone at that point
FRANFORT PLANE: Orbitale-tragion horizontal line

Protocol used for anthropometric measurements: wwwn.cdc.gov/nchs/data/nhanes3/manuals/anthro.pdf

Weight Measurement Protocol

1. Ask participant to wear FHS gown for measurement if he/she brought a heavy gown from home ask them to remove it. The participant should remove slippers or shoes.

2. Prior to asking participant to step onto the scale, lift the counter poise and position it at zero.

3. Ask the participant to step onto the scale, facing measurement beam.

4. Instruct the participant to stand in the middle of the scale platform with head erect and eyes looking straight ahead. Weight should be equally distributed on both feet and the participant should not touch or support him/herself.

5. With the participant standing still in the proper position lift the counterweight (larger weight) and slide it to the right until the beam approaches balance.

6. Adjust the top poise until the beam is evenly balanced.

7. Have the participant step off the scale. The technician should stand directly in front of the scale and read the weight with eyes level to the point of measurement.

8. Record the weight to the nearest pound; **round up if ≥ 0.5, round down if < 0.5**.

9. If deviations from the protocol occur record it as a protocol modification.

Equipment and Calibration For Height and Weight

1. Scale to measure body weight in lbs.:
   Worcester Scale Co., Inc.
   228 Brooks Street
   Worcester, MA
   508-853-2886

2. Weights to calibrate scale: One 50 lb weight and two 25 lb weights
   Worcester Scale Co., Inc. (See address above)

3. Accu Hite Stadiometer
   Quick Medical
   425-831-5963
   888-345-4858

Annual/Monthly/Daily Height and Weight Equipment Calibration Protocol

Activity	Daily	Weekly	Monthly	Yearly
Scale				
Zero Reading	**X**			
50# Weight			**X**	
Professionally Calibrated				**X**
Stadiometer				
Check Level with Calibration Tape			**X**	

1. **Scales: Annually/Monthly/Daily (during clinic)**

   Protocol:

   Daily:

   a. To balance scale, move both poises to zero. If not balanced, turn balance screw to right or left until scale balances.

   Monthly:

   b. Once a month scales are to be calibrated.
   c. Set both poises at zero
   d. Place a 50 lb weight onto the scale.
   e. Set bottom poise to 50 (top poise at 0).
   f. If scale is balanced then calibration is done.
   g. If not balanced, turn balance screw to right or left until scale balances.
   h. Set top poise to 50 (bottom poise at 0)
   i. If scale is balanced then calibration is done.
   j. If not balanced, turn balance screw to right or left until scale balances..
   k. Mark the date in the calibration log book located in the clinic office.
   l. Scales must be certified on a yearly basis. This information can be found in the Clinic Equipment Book located in the clinic office.

2. **Stadiometers: Monthly**

Protocol:

a. Using the purple measuring tape located in the Center Float Desk drawer.
b. Line up against the meter to determine correct marker points.
c. Make sure to move up and down at different spots along the meter.
d. If lines do not match up then a new stadiometer must be ordered.
e. Check the Level in the end of the sliding piece.
f. If level is uneven then it needs to be adjusted.
g. Mark date in calibration log book once a month.

SCALE
Daily Calibration Log
Room #

Year / Month	**Mon** Zero reading	**Tues** Zero reading	**Wed** Zero reading	**Thurs** Zero reading	**Fri** Zero reading

SCALE and STADIOMETER
Monthly Calibration Log
Room #

Year	JAN.	FEB.	MARCH	APRIL	MAY	JUNE
Stadiometer						
Scale						

Year	JULY	AUG	SEPT	OCT	NOV	DEC
Stadiometer						
Scale						

Training and Certification of Staff

New Staff

- Given Protocol to read, understand, ask questions to Supervisor
- Protocol is demonstrated by Supervisor
- New Staff observes other Techs performing Protocol
- New Staff practices Protocol on staff and volunteers
- New Staff performs Protocol on participant with Supervisor or Certified Tech observing
- When Supervisor feels New Staff is proficient in Protocol, Supervisor will certify New Staff
- Certified New Staff will perform Protocol on own
- Certification date is noted in Certification Log

Recertification of Staff

- Occurs when there is a major deviation on Supervisor Observations or a new study with a new protocol is introduced into the exam
- Protocol is demonstrated by Supervisor
- Staff observes other Techs performing Protocol
- When Supervisor feels Staff is proficient in Protocol, Supervisor will recertify Staff
- Recertification date is noted in Certification Log

Quality Control

In order to maintain the quality of the data, every 8 weeks, each technician that performs anthropometric measures must complete quality control measurements.

This is done for:

1) Waist and Hip
2) Height and Weight

Height and Weight

Each technician, paired with another technician and out of each other's view, performs each height and weight measurement.

Height: Record in inches rounded down to the nearest ¼ inch
Weight: Record in whole pounds recorded to nearest pound. Round up if ≥ 0.5, round down if < 0.5

If the difference in height is more than .25 inches, the measurement is repeated.
If the difference in weight is more than 1 pound, or the average of .5 pound, the measurement is repeated.

If the difference cannot be resolved, recertification with techs is performed.

Supervisor Observations performed quarterly

QC Reports with summary of measurements done by technician prepared by Data Management

Date: _____ **Tech ID#_____**

Supervisor:_____ **Participant_____**

Standing Height Measurement
Supervisor Checklist

Check that each procedure is carried out correctly. Check yes if correct or no if incorrect. Provide an explanation of the incorrect item. Items are presented in the sequence of the examination procedure, but may require confirmation before or after the exam.

Yes	No	Standing Height Measurement
		The participant should be barefoot or wearing thin socks so positioning of the body can be seen. Ask participant to stand erect with his/her back to vertical mounted stadiometer.
		Heels should be together and against the vertical ruler, both feet flat on the floor, with weight distributed evenly across both feet. Check to make sure both feet are back against the wall.
		Participant faces straight ahead with his/her head positioned in the Frankfort horizontal plane. The lower margin of the bony orbit (the socket containing the eye) should be on the same horizontal plane as the most forward point in the supratragal notch (the notch just above the anterior cartilaginous projections of the external ear).
		Ask participant to let arms hang freely by the sides of the trunk, palms facing the thighs. Ask participant to inhale deeply and maintain a fully erect position.
		Bring the level down snugly (but not tightly) on top of participant's head. Use an extension board for proper measurement of severely kyphotic subjects.
		Record measurement to the **nearest 1/4 inch, rounding down.**

Yes	No	Deviations
		Did the tech perform any minor deviations?
		Did the tech perform any major deviations?
Comments/Corrections/Deviations:		
Supervisor Initials:		
Date:		

Date: _____ **Tech ID#_____**

Supervisor:_____ **Participant_____**

Weight Measurement
Supervisor Checklist
Clinic

Check that each procedure is carried out correctly. Check yes if correct or no if incorrect. Provide an explanation of the incorrect item. Items are presented in the sequence of the examination procedure, but may require confirmation before or after the exam.

Yes	No	Weight Measurement
		Ask participant to wear FHS gown for measurement if he/she brought a heavy gown from home. The participant should remove slippers or shoes.
		Prior to asking the participant to step onto the scale, lift the counter poise and position it at zero.
		Ask the participant to step onto the scale, facing measurement beam.
		Instruct the participant to stand in the middle of the scale platform with head erect and eyes looking straight ahead. Weight should be equally distributed on both feet, and participant should not touch or support him/herself.
		With the participant standing still in the proper position, lift the counterweight (larger weight), and slide it to the right until the beam approaches balance.
		Adjust the top poise until the beam is evenly balanced.
		Have the participant step off the scale. The technician should stand directly in front of the scale and read the weight with eyes level to the point of measurement.
		Record the weight to the nearest pound; **round up if ≥ 0.5, round down if < 0.5**.

Yes	No	Deviations
		Did the tech perform any minor deviations?
		Did the tech perform any major deviations?
Comments/Corrections/Deviations:		
Supervisor Initials		
Date:		

Waist Girth at Umbilicus

1. Participant stands erect, arms hanging loosely at sides, feet together and weight equally distributed on both feet, facing straight ahead. The technician will take the gown from the back and place it over the left shoulder of the participant. The technician will ask the participant to cross their arms over their chest with hands at shoulders and hold the gown in place

2. Apply anthropometric tape at the level of the umbilicus. Roll underpants down below umbilicus if underwear is covering umbilicus.

3. Apply tape snugly but not tightly.

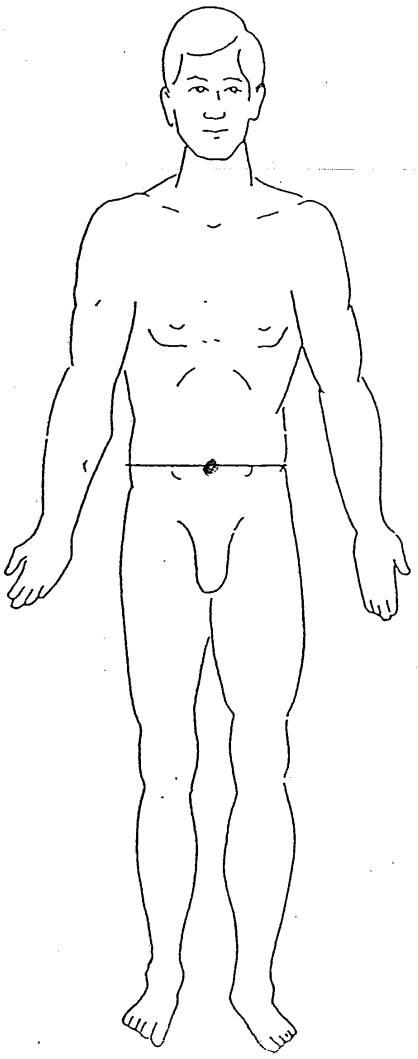
4. Make sure the tape is horizontal and not twisted, checking from both the front and back by using 2 mirrors mounted to the wall.

5. Before recording measurement ask the participant to fully relax their shoulders.

6. Record measurement **to the nearest 1/4 inch, rounding down.**

Protocol used for anthropometric measurements: wwwn.cdc.gov/nchs/data/nhanes3/manuals/anthro.pdf

Waist Girth



Waist Girth at level of umbilicus.

Protocol used for anthropometric measurements: wwwn.cdc.gov/nchs/data/nhanes3/manuals/anthro.pdf

Hip Circumference Measurement

1. Participant stands erect, arms hanging loosely at sides, feet together and weight equally distributed on both feet, facing straight ahead. The technician will take the gown from the back and place it over the left shoulder of the participant. The technician will ask the participant to cross their arms over their chest with hands at shoulders and hold the gown in place.

2. The examiner stands on the participants left side and applies the measuring tape around the maximum extension of the buttocks (see figure on next page).

3. The examiner should be squatting or kneeling so that their eyes are at the level of the maximum extension of the buttocks.

4. Make sure the tape is horizontal and not twisted, checking from both the front and back by using 2 mirrors mounted on the wall.

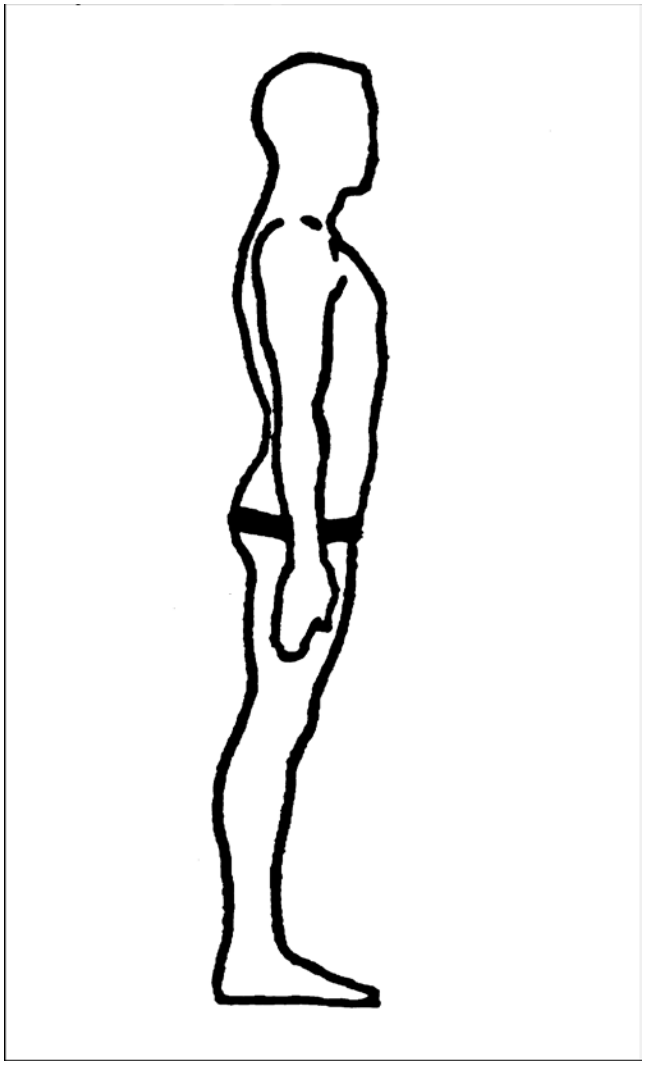
5. The zero end of the tape is held under the measurement value.

6. Apply tape snugly but not tightly.

7. Record measurement **to the nearest ¼ inch, rounding down.**

8. If the participant is wearing baggy underpants then the examiner stands in back and gathers the side seams together and places the thumb in the fabric to make a fold.

Protocol from: National Health and Nutrition Examination Survey III – Body Measurements (Anthropometry)
http://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/NCHS/MANUALS/ANTHRO.PDF



Protocol from: National Health and Nutrition Examination Survey III – Body Measurements (Anthropometry)
http://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/NCHS/MANUALS/ANTHRO.PDF

Date: _____ Tech ID#_____ Quarter: I, II, III, IV (circle one)
Supervisor: Emily Manders Participant Label_____

Anthropometrics

Check that each procedure is carried out correctly. Check yes if correct or no if incorrect. Provide an explanation of the incorrect item. Items are presented in the sequence of the examination procedure, but may require confirmation before or after the exam.

	No	**Hip Circumference**
		Participant stands erect, arms hanging loosely at sides, feet together and weight equally distributed on both feet, facing straight ahead. The examiner tells the participant that she is going to open the robe and place it over the ppt left shoulder. The examiner then asks the ppt to cross arms over chest to hold the robe, standing up straight but shoulders relaxed, weight equally distributed on both feet, facing straight ahead
		The examiner stands on the participants left side and applies the measuring tape around the largest part of the buttocks.
		The examiner then adjusts the sides of the tape and checks the front and sides of the tape measure is horizontal
		The zero end of the tape is held under the measurement value
		Apply tape snugly but not tightly
		Record measurement **to the nearest ¼ inch, rounding down**

Yes	**No**	**Waist Girth Measurement**
		Participant is asked to stand erect with head facing straight ahead. The examiner tells the participant that she is going to open the robe and place it over the ppt left shoulder. The examiner then asks the ppt to cross arms over chest to hold the robe, standing up straight but shoulders relaxed.
		The examiner places the anthropometric tape at the level of the umbilicus, underneath the gown. If underwear is covering the umbilicus, the examiner rolls down the under below the umbilicus.
		Tape is applied snugly but not tightly.
		The examiner checks the tape that it is placed horizontal and not twisted. It is checked from both the front and back using 2 mirrors mounted to the wall.

Date: _____ Tech ID#_____ Quarter: I, II, III, IV (circle one)
Supervisor: Emily Manders Participant Label_____

		Measurement is recorded to the nearest ¼ inch, rounding down.

Yes	**No**	**Deviations**
		Did the tech perform any minor deviations?
		Did the tech perform any major deviations?
Comments/Corrections/Deviations:		
Supervisor Initials:		
Date:		

EIGHT WEEK CYCLE QUALITY CONTROL TRACKING FORM

_____06/28/2021- 08/23/2021_____

TECH ID	HEIGHT/WEIGHT	WAIST	HIP
788/19			
788/960			

TECH ID	HEIGHT/WEIGHT	WAIST	HIP
19/788			
19/960			

TECH ID	HEIGHT/WEIGHT	WAIST	HIP
960/19			
960/788			

TECH ID	HEIGHT/WEIGHT	WAIST	HIP

MONTHLY/ANNUALLY CALIBRATIONS-2019-2021

Year / Month	SEPT	OCT	NOV	DEC	JAN 2020	FEB
Room 102 (ECG)						
Stadiometer Level						
Scale						
Measuring Tape						
Hand Grip						
Room 103 (ECG)						
Stadiometer Level						
Scale						
Measuring Tape						
Hand Grip						
Room 114 (ECG)						
Stadiometer Level						
Scale						
Measuring Tape						
Hand Grip						
Room 109 (MD)						
Manometer						
Room 107 (MD)						
Manometer						

	MAR 2020	APR	MAY	JUNE	JULY	AUG
Room 102 (ECG)						
Stadiometer Level						
Scale						
Measuring Tape						
Hand Grip						
Room 103 (ECG)						
Stadiometer Level						
Scale						
Measuring Tape						
Hand Grip						
Room 114 (ECG)						
Stadiometer Level						
Scale						
Measuring Tape						
Hand Grip						
Room 109 (MD)						
Manometer						
Room 107 (MD)						
Manometer						

CES-D Scale

A. Rationale and Background:

The Center for Epidemiologic Studies Depression Scale (CES-D) was developed for use in epidemiologic research of depressive symptomatology in the general population. It was designed as a screening instrument to elicit symptoms associated with depression. It is intended to document the presence and severity of depressive symptoms but is not intended to make clinical diagnosis. It assesses the current state of the subject by focusing on symptomatology in the past week.

Note: The depression questions used in the NHANES 1 survey were the 20-item set of the CES-D developed and validated by the Center for Epidemiologic Studies, National Institute of Mental Health (NIMH).

The scale is given at each exam. The scale is not given if the patient is: sedated, aphasic, non-English speaking, or uncooperative.

B. Procedure:

1. Each question is read to the participant who responds with one of four answers.

2. Response alternatives should be printed on paper which is placed in front of the participant for reference.

3. Each category of response should be explained to the participant prior to administering the scale.

4. If the participant is unable to read the response sheets, the interviewer should read each response as well as the question referring to their feelings in the past week.

5. Be sure the participant understands that the questions refer to his/her feelings only during the past week.

C. CES-D Scoring:

Each item has a range of four response options which indicated how often the survey examinee had felt that way during the past week:

Response Option

Rarely or none of the time (less than 1 day)

Some or a little of the time (1-2 days)

Occasionally or a moderate amount of the time (3-4 days)

Most or all of the time (5-7 days)

Questionnaire items 4, 8, 12, and 16 were worded in a positive (i.e., nondepressed) direction. The other 16 scale items were worded in a negative direction to elicit depressive symptomatology directly. To score the CES-D, the sense of the fours positive questionnaire items was reversed by subtracting their coded value (indicating the response option selected) from 3. Then the coded values for all 20 items were summed into a total score. The range of possible scores was 0-60. The final score is calculated by the computer.

D. Methods:

The CES-D Questionnaire consists of 20 questions. Since it is a scale for depression, it must be completed using responses by the participant, not a proxy.

SCRIPT: *The questions below ask about your feelings. For each of the following statements, please say if you felt that way during the past week.*

1. Hand the response sheet to the participant and explain the response options. The following definitions should be given:

   Code
   Rarely or none of the time (< one full day)
   Some or a little of the time (1 to 2 days in the past week)
   Occasionally or moderate amount of time (3 to 4 days in the past week, or about 1/2 the time)
   Most of the time (5 to 7 days in the past week)

   If participant answers *YES* to a given statement, repeat the above responses to get a correct answer.

2. Read each item as it is written on the form. Preface statements 1, 6 & 11 with the statement *During the past week*, then continuing with the response categories. For example:

SCRIPT: *During the past week I was bothered by things that usually don't bother me. Did you feel that way rarely or none of the time, some or a little of the time, occasionally or moderate amount of time, or most or all of the time?*

Question 1: During the past week I was bothered by things that usually don't bother me.

Question 6: During the past week I felt depressed.

Question 11: During the past week my sleep was restless

****Note: Emphasize to the participant that it is only the past 7 days.****

3. Discontinue reading the responses when the participant provides a response before you are finished. On the next item, however, again begin to read the entire set of responses.

4. Code **9** = *Refused* or *Do not know* is used when:

   a. The question was asked, but the participant chooses not to answer. For example, response was *I would rather not say,* or *Go on to the next question*.
   b. The question was asked, but the participant does not know, does not remember, or does not understand the statement.

** If "unknown" is used more than 4 times on the questionnaire it is no longer considered valid for research. Do your best to have the participant give you an answer listed on the response key.**

5. Press on the response on the form in Redcap.

6. When the participant asks about the meaning of any item or tries to qualify a statement, simply repeat the statement. For example:

   Participant: *What do you mean by bothered?*

   Interviewer: *I was bothered by things that usually don't bother me. Did you feel that way rarely or none of the time, some or a little of the time, occasionally or moderate amount of time, or most or all of the time during the past week?*

7. When the participant still asks about the meaning or says he/she does not understand, check **9** = refused or do not know. Do not try to interpret the statement for the participant.

Date:_____ Tech ID #_____ Quarter:_____
Supervisor:_____ Participant label:_____

CES-D Supervisor Checklist

Check that each procedure is carried out correctly. Check yes if correct or no if incorrect. Provide an explanation of the incorrect item. Items are presented in the sequence of the examination procedure, but may require confirmation before or after the exam.

Yes	No	CES-D
		SCRIPT: *The questions below ask about your feelings. For each of the following statements, please say if you felt that way during the past week.*
		Hand the response sheet to the participant and explain the response options. The following definitions should be given: Code Rarely or none of the time (< one full day) Some or a little of the time (1-2 days) Occasionally or moderate amount of time (3-4 days) Most of the time (5-7 days)
		Read each item as it is written on the form, prefacing questions 1, 6 and 11 with the statement *During the past week*, and then continuing with the response categories.
		Press the response on the form in Redcap
		When the participant asks about the meaning of any item or tries to qualify a statement, simply repeat the statement.
		If the participant is unable to read the response sheets, the interviewer should read each response as well as the question referring to their feelings in the past week.

Yes	No	Technician Review
		Did the technician introduce the set of questions with clear explanation?
		Did the technician ask the questions exactly as written on the form?
		Did the technician correctly clarify any questions the participant had?
		Did the technician score the participant's responses correctly?
		Did the technician review the form for completeness?

Date:_____ Tech ID #_____ Quarter:_____
Supervisor:_____ Participant label:_____

CES-D Supervisor Checklist

Yes	**No**	**Deviations**
		Did the tech perform any minor deviations?
		Did the tech perform any major deviations?
Comments/Corrections/Deviations:		
Supervisor Signature:		
Date:		

Rarely or none of the time (Less than 1 day)

Some or a little of the time (1-2 days)

Occasionally or moderate amount of time (3-4 days)

Most or all of the time (5-7 days)

Guidelines for Administering the Physical Activity Scale for the Elderly Questionnaire (PASE)

The PASE is an instrument that measures the level of physical activity for individuals aged 65 and older. The PASE is comprised of self-reported occupational, household and leisure items over a one-week period and can be administered by telephone, mail or in-person. The FOS Exam 9 musculoskeletal technologist will administer The PASE using an electronic questionnaire on the web-based REDCap system. If REDCap is unavailable, responses will be recorded by the technologist on the identical paper questionnaire, v3.0 OP Questionnaire, and then enter the responses in REDCap within 24 hours of system availability.

The PASE scoring was derived from movement counts from an electronic physical activity monitor, activity diaries and self-assessed activity levels in a general population of non-institutionalized older persons. The PASE can be used to measure physical activity in surveys of older persons and to assess the effectiveness of interventions. The leisure activity items require participants to first report the number of days per week the activity was performed and then the number of hours per day. PASE scores are calculated from weights and frequency values for each of the 12 types of activities. Responses to the first question about sitting are not scored. The validity and reliability of PASE were established in a random sample of 222 individuals ages 65-100y, and scores were significantly correlated with balance, grip strength, leg strength and health status. Scores range from 0 to 361. A general population (from NERI) had mean score of 103 (SD 64.1). Means by age groups were:

	65-69y	**70-75 y**	**76-100y**
MEN	144.3 ± 58.6	102.4 ± 53.7	101.8 ±45.7
WOMEN	112.7 ± 64.2	89.1 ± 55.5	62.3 ±50.7

General Queries and Prompts

If a participant asks about the last 7 days, you can clarify: e.g., if today is Tuesday and participant asks about the time frame, then you could say "that is, since LAST Tuesday". If participant gives response that is not echoing responses listed, refer back to the responses on the questionnaire (e.g., if a participant answers "I do that every day" to the how-often items, repeat the possible responses until participant chooses one category. Alternatively for the how-many-hours items, if a participant answers "I do it all day long", again refer back to the responses on the questionnaire). If a participant answers "5 hours" or a number larger than 4, you can check the box "More than 4 hours" rather than making the participant state category specifically. If a participant refers to a timeframe that is not within past 7 days (e.g., I did activity two weeks ago or a month ago), refer him/her back to the past 7 days.
Appendix C lists extensive examples of applicable activities for each of the activity levels queried in the following items. If it is unclear as to what level an activity should be coded, refer to the list. If an activity is not on the list and it is not clear where it should be included in the PASE, write appropriate notes in the questionnaire (e.g., square-dancing twice week for 3 hours each time).

Q1. Over the past 7 days, how often did you participate in sitting activities such as reading, watching TV, or doing handcrafts?

Visiting with others, sewing, paperwork, playing musical instruments, playing cards, and/or bingo are considered sitting activities.
Example: The participant watches TV every day, code sitting activities as often (5-7 days)

Q1b. On average, how many hours per day did you engage in these sitting activities?
The two items that ask about sitting activity are for the participant to think of activities and time spent. However, these items are not included in the PASE scoring of overall physical activity.

Q2. Over the past 7 days, how often did you take a walk outside your home or yard for any reason? For example, for fun or exercise, walking to work, walking the dog, walking in a mall, etc?

This level of activity includes treadmill walking**.** See Appendix A for other applicable activities. Any specific leisure time, household or work related activity that involves walking is coded entirely under the appropriate activity category (light, moderate, or strenuous sport and recreation, muscle strength and endurance, or work related). Hence, walking as part of golf would be coded only as moderate sport and recreation (see other item) and not as walking. A key component here is walking outside the home, so if a participant says "I walk around my building", leaving the apartment or flat is important, but only if leaving the home area. Walking to the mailbox or mail area is NOT walking outside the home (typically, unless a rural area). Walking within the participant's yard is not included.
Example: The participant walks three times a week, 3-4 times each day for 15 minutes. Throughout the PASE, the number of days rather than the number of occasions is coded. Therefore, the participant walked sometimes (3-4 days).

Q2a. On average, how many hours per day did you spend walking?

Example: The participant walks 30 minutes to 1.5 hours per day. The average time spent walking was 1 hour. Code 1 but less than 2 hours per day.

Q3. Over the past 7 days, how often did you engage in light sport or recreational activities such as bowling, golf with a cart, shuffleboard, fishing from a boat or pier or other similar activities?
Example: The participant plays golf 4 days per week for 4 hours/day. Three days a week, the golfer uses a power cart. One day a week, the golfer walks the course either pulling a cart, carrying the clubs or the caddy carries the clubs. Only golf with a power cart would be coded under light sport and recreation. Specifically, the participant golfed with a cart sometimes (3-4 days/week) for 2-4 hours/day. Golfing without a cart would be marked under moderate sport and recreation as seldom (1-2) days for 2-4 hours/day. Putting or hitting golf balls at a driving range are coded for light sport and recreation. Stretching is not coded under any activity category in the PASE.

Q3b. On average, how many hours per day did you engage in these light sport or recreational activities?
Example: The participant golfs using a power cart 3 days a week for 2-4 hours a day. Code 2-4 hours.
If a participant considers an activity "LIGHT Sport/Recreational" that Appendix E or an example on the questionnaire places in a different category, **THE PASE CATEGORY IS USED AND NOT THE RESPONDENT'S CHOICE**. For example, a participant swims laps and considers this activity Light rather than Strenuous Sport & Recreation. Swimming laps is coded a Strenuous Activity regardless of the respondent's assessment of the activity's intensity. Appendix E lists pre-assigned categories of activities.

Q4. Over the past 7 days, how often did you engage in moderate sport or recreational activities such as doubles tennis, ballroom dancing, hunting, ice skating, golf without a cart, softball or other similar activities?
This level of activity includes most types of dancing, square dancing, ballet, social as well as ballroom dancing listed above**.** See Appendix E for applicable activities.
Gardening and lawn work are not coded under leisure time activities. Gardening and lawn work are considered household activities. Q9b addresses lawn work and Q9c pertains to gardening.

Q4b. On average, how many hours per day did you engage in these moderate sport or recreational activities?

Q5. Over the past 7 days, how often did you engage in strenuous sport or recreational activities such as jogging, swimming, cycling, singles tennis, aerobic dance, skiing (downhill or cross country or other similar activities?
Example: The participant swims laps but considers the activity light rather than strenuous sport and recreation. This participant would get coded into this category. As noted above, swimming laps is coded a strenuous sport and recreational activity regardless of the participant's assessment of the activity's intensity. See Leisure time activities categories in Appendix E.

Q5b. On average, how many hours per day did you engage in these strenuous activities?
Example: The participant takes a one-hour aerobics class, 3 days per week. The class consists of 20 minutes of stretching and 40 minutes of aerobic dance. The 40 minutes of aerobic dance would be coded under strenuous activities. The 20 minutes of stretching would not be coded under any activity category. Under strenuous activities, the interviewer would choose less than one hour a day for 3-4 days per week.
Climbing stairs as part of an exercise regimen is coded under strenuous sport and recreation. However, stair climbing as part of daily activities is not coded in the PASE.

Q6. Over the past 7 days, how often did you do any exercises specifically to increase muscle strength or endurance, such as lifting weights or pushups, etc?
Strenuous work activity, such as moving furniture, is not included in this question. Only activities that are done specifically to increase muscular strength and endurance are used in this question.

Q6a. On average, how many hours per day did you engage in exercises to increase muscle strength or endurance, such as lifting weights, pushups, or physical therapy with weights, etc.?
The exercise activities also may include isometrics. Physical therapy with weights includes hand-held weights and resistance therapy bands.

Q7. During the past 7 days, have you done any light housework, such as dusting, washing or drying dishes, or ironing?
Drying dishes, clothes washing, ironing, hanging up laundry, taking out the garbage and preparing meals are considered light housework. See Appendix E for applicable activities.

Q8.During the past 7 days, have you done any heavy housework or chores such as vacuuming, scrubbing floors, washing windows, or carrying wood?

This level of activity includes moving heavy boxes**.** Stacking wood as a household chore is considered to be heavy housework. See Appendix A for applicable activities.

Q9a. During the past 7 days, did you engage in home repairs like painting, wallpapering, electrical work, etc.?
Home repair includes home improvement and maintenance projects such as painting, plumbing, and carpentry. See Appendix E for applicable activities.

Q9b. During the past 7 days, did you engage in lawn work or yard care, including snow or leaf removal, chopping wood, etc?
Snow removal (sweeping snow, shoveling snow or using a snow blower) is considered to be lawn work or yard care. Lawn mowing is counted as lawn work regardless of the type of mower (riding, power or push) used. Chopping wood outdoors should be coded in this item.

Q9c.During the past 7 days, did you engage in outdoor gardening?
Example: Participant does outdoor gardening in season. In February, the participant has not yet started the garden yet. In this example, Outdoor gardening is coded "no." Only activities performed during the past seven days are coded. If the participant does not have a garden, the item is coded "no".

Q9d. During the past 7 days, did you engage in caring for another person such as a child, dependent spouse, or another adult?
Dependency is defined as a person requiring assistance with activities of daily living (food preparation, personal hygiene, household cleaning). Division of labor within a household (i.e. meal preparation, laundry, yard work) is not considered dependency.
Babysitting is included in this item. Babysitting is not included in Q10 (below) as a work related activity. Pet care is not considered part of this item.

Q10. During the past 7 days, did you work for pay or as a volunteer?
Only work (paid or volunteer) performed during the past 7 days is coded.

Q10a.How many hours per week did you work for pay and/or as a volunteer?
Participants should be encouraged to give their best estimate of the number of hours they worked during the previous seven days. However, if a range of hours is reported (e.g. 15-20 hours), use the midpoint of the range as an estimate.
If a participant did both paid and volunteer in past 7 days, sum the number of hours.

Q10b.Which of the following categories best describes the amount of physical activity required on your job and/or volunteer work?
Category 1("Mainly sitting with slight arm movements") includes examples such as: office worker, watchmaker, seated assembly line worker, bus driver, etc.
Category 2("Sitting or standing with some walking") includes examples such as: cashier, general office worker, light tool and machinery worker.
Category 3("Walking, with some handling of materials generally weighing less than 50 pounds" includes examples such as: mailman, waiter/waitress, construction worker, heavy tool and machinery worker.
Category 4("Walking and heavy manual work often requiring handling of materials weighing over 50 pounds") includes examples such as: lumberjack, stonemason, farm or general laborer].

If the participant indicates two categories of physical activity required on the job or volunteer work, the higher rather than lower activity levels are coded.
Example: The participant works half the time sitting or standing with some walking, and the other half of the time walking, with some handling of materials.

Never

Seldom, 1-2 days

Sometimes, 3-4 days

Often, 5-7 days

Unknown

Less than 1 hour

1 hour but less than 2 hours

2-4 hours

More than 4 hours

Unknown

Administration of Physical Activity Questionnaire
Rest and Activity for a Typical Day

NOTE: This questionnaire was only used from 10/22/2019-12/09/2019

1. Hand participant a copy of the Physical Activity Questionnaire (24 hour).

2. Explain that the first section is Rest and Activity for a Typical Day (24 hours).

3. The day is broken up into different types of activities and a typical day is considered MOST days of the week.

4. Read through each activity and do NOT clarify.
    - **Sleep**
        - Example: napping during the day and actual night sleep.
    - **Sedentary**
        - Example: sitting in the car, eating meals, TV, computer, etc.
    - **Slight Activity**
        - Example: walking to the car, shopping, standing in line, etc.
    - **Moderate Activity**
    - **Heavy Activity**

    Explain that a total number of hours for a typical day must equal 24 hours.*

5. This should capture over the past year.

6. Make adjustments according to participant until the total number of hours equals 24*.

    * If the total hours the participants states does not equal to 24 on the first pass, please ask the participant where he/she might have underestimated the hours stated. Do not just add missing hours to the last activity automatically. The participant needs to clarify the activity amounts until they add up to 24.

Administration of Physical Activity Questionnaire
Time Spent Doing Sitting Activities

Explain that now you will be asking 2 questions about *sitting* activities, in particular.

1. *Over the past 7 days, how often did you participate in SITING ACTIVITIES such as reading, watching TV, using the computer or doing handcrafts?*

Read through each **response level:**

Never, code as 0
Seldom/1-2 days, code as 1
Sometimes/3-4 days, code as 2
Often/5-7 days, code as 3
If refused to answer, code as 8
If answer **Don't Know/Unknown** code as 9

2. *Over the past 7 days, how many hours per day did you engage in these activities?*

Read through each **response level:**

Less than 1 hour, code as 1
1 hour but less than 2 hours, code as 2
2-4 hours, code as 3
More than 4 hours, code as 4
If refused to answer, code as 8
If answer **Don't Know/Unknown** code as 9

Administration of Physical Activity Questionnaire
Time Spent Actually Doing the Activity

This section of physical activity questions was adapted from the Cardiovascular Health Study (CHS). http://128.208.129.3/chs/forms/4pl.htm They cover physical activity over the past year.

Introductory Script:
Now I am going to read you a list of activities. Please tell me which activities you have done in the past year.

In the past 12 months did you (do) the following activity in any month?

1. Read through each activity.

    a. If answered NO, move to next question.

    b. If answered YES, move below to answer,

        i. In a typical 2 week period of time, how often did do this activity?
        ii. How long did you do this activity on average each session? *(# of hours and/or minutes*)
        iii. How many months out of the year did you do this activity?

    c. If REFUSED, code as 8\

    d. If answered UNKNOWN, code as 9

    e. Regarding the last row for "Other" activity not listed above, it is acceptable to cue the participant to other possibilities, such as skiing, horseback riding, etc.

****NOTE: If golfing is done with a cart, code under light sport or recreational activities.**

NOTE: This questionnaire was only used from 10/22/2019-12/09/2019

Date: _____ Tech ID#_____ Quarter: I, II, III, (circle one)
Supervisor: Emily Manders Participant Label_____

Yes	No	Physical Activity – Part One
		The tech explains that the question is Leisure time Activities in the past 7 days
		The tech explains Sitting, Walking for exercise, Sports and Recreational Activities and Strength Endurance exercise
		Examples are given
		The tech does not coach them or help them fill answers.

Yes	No	Technician Review
		Did the technician introduce the set of questions with clear explanation?
		Did the technician ask the questions exactly as written on the form?
		Did the technician correctly use the answer key?
		Did the technician correctly clarify any questions the participant had?
		Did the technician score the participant's responses correctly?
		Did the technician review the form for completeness?

Yes	No	Deviations
		Did the tech perform any minor deviations?
		Did the tech perform any major deviations?
Comments/Corrections/Deviations:		
Supervisor Initials:		
Date:		

Rosow-Breslau Questions

A. Rationale & Background

Respondents' self-assessments of health may raise questions about the validity of such judgments. However, we are not interested in the literal details of people's medical condition as much as in the behavioral consequences, their physical capacity for role fulfillment and social participation. We are primarily concerned with the *functional* health which old people report, i.e., the degree to which they claim they can manage adequately or are restricted in their activities because of their physical condition or capacity. *Breslau, M, Rosow, I: A Guttman Health Scale for the Aged. 556-559*

B. Methods

The method of assessing physical functioning is **self-report**. The questions assess the degree of difficulty that a person has performing a specific activity. This form has several important purposes:

1. This data will enable us to assess the level of independence and function in the study population.
2. It is hypothesized that impairments of physical function may be a risk factor for cardiovascular end points and progression of disease.
3. It will measure loss of physical functioning as a consequence of cardiovascular disease.

C. Procedures

Questions:

Coding
No, unable to do
Yes, independent
Does not do
Unknown

1. *Are you able to do heavy work around the house, like shovel snow or wash windows, walls, or floors without help?* (Scrub floors, wash windows, rake leaves, and mow lawn).

2. *Are you able to walk half a mile without help?* (Walk one half mile or 4-6 blocks without stopping for more than 5 minutes).

3. *Are you able to walk up and down one flight of stairs without help?*

Date:_____ Tech ID #_____ Quarter:_____
Supervisor:_____ Participant label:_____

Rosow-Breslau Supervisor Checklist –
Generation 3

Check that each procedure is carried out correctly. Check yes if correct or no if incorrect. Provide an explanation of the incorrect item. Items are presented in the sequence of the examination procedure, but may require confirmation before or after the exam.

Yes	No	Rosow-Breslau Questions
		Are you able to do heavy work around the house, like shovel snow or wash windows, walls, or floors without help? (Scrub floors, wash windows, rake leaves, mow lawn).
		Are you able to walk half a mile without help? (Walk one half mile or 4-6 blocks without stopping for more than 5 minutes).
		Are you able to walk up and down one flight of stairs without help?

Yes	No	Technician Review
		Did the technician introduce the set of questions with clear explanation?
		Did the technician ask the questions exactly as written on the form?
		Did the technician correctly clarify any questions the participant had?
		Did the technician correctly use the answer key?
		Did the technician enter the participant's responses correctly in Redcap?
		Did the technician review the form for completeness?

Yes	No	Deviations
		Did the tech perform any minor deviations?
		Did the tech perform any major deviations?
Comments/Corrections/Deviations:		
Supervisor Signature:		
Date:		

KATZ-Activities of Daily Living

Tech-Administered

A. Background and Rationale:

This section is designed to assess the following spectrum of physical functioning. This section assesses:

- Ability to carry out activities of daily living

s

B. Activities of Daily Living

The activities & examples of each ADL include:

1. Dressing
   - Undressing and redressing
   - Devices such as: velcro, elastic laces.
2. Bathing
   - Including getting in and out of tub or shower
   - Devices such as: bath chair, long handled sponge, hand held shower, safety bars.
3. Eating
   - Devices such as: rocking knife, spork, long straw, plate guard.
4. Transferring
   - Getting in and out of a chair
   - Devices such as: sliding board, grab bars, special seat.
5. Toileting activities
   - Using the bathroom facilities and handling clothing
   - Devices such as: special toilet seat, commode.

NOTE: With a nursing home visit, the participant's chart may be used to verify or to obtain accurate information on ADL's. If information is obtained from the nursing home staff then proxy information on screen must be completed.

Yes	No	Katz ADLs
		SCRIPT: *During the Course of a Normal Day, can you do the following activities independently or do you need help from another person or use special equipment or a device?*
		Tech goes through each activity: ▪ Dressing (undressing and redressing) *Devices such as: Velcro, elastic laces* ▪ Bathing (including getting in and out of a tub or shower) *Devices such as: bath chair, long handled sponge, hand held shower, safety bars* ▪ Eating *Devices sucha as: rocking knife, spork, long straw, plate guard* ▪ Transferring (getting in and out of a chair) *Devices such as: sliding board, grab bars, special seat* ▪ Toileting Activities (usuing bathroom facilities and handle clothing) *Devices such as: special toilet seat, commode*
		Tech codes responses correctly: ▪ 0=No help needed, independent ▪ 1=Uses device, independent ▪ 2=Human assistance needed, minimally dependent ▪ 3=Dependent ▪ 4=Does not do during a normal day ▪ 9=Unknown

Yes	*No*	***Technician Review***
		Did the technician introduce the set of questions with clear explanation?
		Did the technician ask the questions exactly as written on the form?
		Did the technician correctly use the answer key?
		Did the technician correctly clarify any questions the participant had?
		Did the technician enter the participant's responses correctly in RedCap?
		Did the technician review the form for completeness?

Yes	No	Deviations
		Did the tech perform any minor deviations?
		Did the tech perform any major deviations?
Comments/Corrections/Deviations:		
Supervisor Initials:		
Date:		

Nagi Questionnaire

Tech-Administered

1. Show and explain the answer key *before* administering the questionnaire. The participant is to choose one of the following answers for each activity:

    0 = No Difficulty
    1 = A Little Difficulty
    2 = Some Difficulty
    3 = A Lot of Difficulty
    4 = Unable to Do
    5 = Don't Do on Physician or Health Care Providers Orders
    6 = I don't know
    9 = Unk. (either Tech. forgot to administer or ppt. refused to answer)

2. Start with, *For each activity, tell me whether you have No Difficulty, A little Difficulty, Some Difficulty, A Lot of Difficulty, if you are Unable to do it, if you Do not do it on Physician or Health Care Providers Orders, or if you don't know.*

3. Read each activity separately, and go through the level of difficulty for each one until the participant understands the response choices.

Do not ask these questions if the participant is cognitively impaired; proxy may answer these questions.

No Difficulty

A Little Difficulty

Some Difficulty

A Lot of Difficulty

Unable to Do

Don’t Do on Physicians or Health Care Providers Orders

Yes	No	Nagi Questions
		Show and explain the answer key *before* administering the questionnaire ▪ No difficulty ▪ A little difficulty ▪ Some difficulty ▪ A lot of difficulty ▪ Unable to do ▪ Don't do on physician or health care provider orders ▪ Don't know ▪ Unknown
		Tech goes through each activity & codes correctly
Yes	***No***	***Technician Review***
		Did the technician introduce the set of questions with clear explanation?
		Did the technician ask the questions exactly as written on the form?
		Did the technician correctly use the answer key?
		Did the technician correctly clarify any questions the participant had?
		Did the technician enter the participant's responses correctly in RedCap?
		Did the technician review the form for completeness?

Yes	No	Deviations
		Did the tech perform any minor deviations?
		Did the tech perform any major deviations?
Comments/Corrections/Deviations:		
Supervisor Initials:		
Date:		

No Difficulty

A Little Difficulty

Some Difficulty

A Lot of Difficulty

Unable to Do

Don’t Do on Physicians or Health Care Providers Orders

Technician Administered Questionnaire

Please see annotated forms for the following Questionnaires:

- Sociodemographic Questionnaire
- Respiratory Disease Questionnaire
- Fracture Questionnaire

Supervisor Observations for Respiratory Questionnaire

Yes	No	
		Respiratory questionnaire is administered. Questions are asked exactly as they are listed on the page.

Yes	No	Technician Review
		Did the technician introduce the set of questions with clear explanation?
		Did the technician ask the questions exactly as written on the form?
		Did the technician correctly clarify any questions the participant had?
		Did the technician correctly use the answer key?
		Did the technician score the participant's responses correctly?
		Did the technician review the form for completeness?

Yes	No	Deviations
		Did the tech perform any minor deviations?
		Did the tech perform any major deviations?

Comments/Corrections/Deviations:

Supervisor Signature:	Date:

Yes	*No*	***Technician Review***
		Did the technician introduce the set of questions with clear explanation?
		Did the technician ask the questions exactly as written on the form?
		Did the technician correctly use the answer key?
		Did the technician correctly clarify any questions the participant had?
		Did the technician enter the participant's responses correctly in RedCap?
		Did the technician review the form for completeness?

Yes	**No**	**Deviations**
		Did the tech perform any minor deviations?
		Did the tech perform any major deviations?
Comments/Corrections/Deviations:		
Supervisor Initials:		
Date:		

Gen 2 Exam 10 Omni 5 Proxy Form
(Research Center & Offsite)

Proxy Information

Whenever someone else is providing information about a participant that is collected on the forms, this person is considered a "proxy". When an offsite visit is to a nursing home, frequently a nurse familiar with the participant will be the proxy. Sometimes during offsite exams there will be more than one proxy. For example a Home Health Aid may answer all of the questions relating to ADL's, and the daughter may answer all of the medical questions. In cases like these, record information for both proxies on the proxy sheet in the exam form.

Important: The proxy that is designated by the participant as their FHS proxy does not have to be the same person as the one listed on the exam form.

APPENDIX A:
ACTIVITY CATEGORIES

Light Sport and Recreation

archery
badminton
billiards
boating (canoeing, rowing sailing)
bocci
bowling
catch
croquet
darts
fishing
frisbee
golf with a power cart
horseshoes
musical program
riflery
shuffleboard
swimming: no laps
table tennis

Moderate Sport and Recreation

barn chores
dancing (ballroom, ballet, disco)
fencing
football
golf without a cart
horseback riding
scuba diving
skating (ice, roller)
sledding
snorkeling
softball / baseball / cricket
surfing
tennis (doubles)
trampoline
volleyball

Light Housework

drying dishes
dusting
hanging up laundry
ironing
laundry
meal preparation
washing dishes

Strenuous Sport and Recreation

aerobic dance or water aerobics
backpacking
baseball
bicycling / exercise bike
board sailing
handball / paddleball
racquetball
hiking
hockey (ice or field)
jogging
lacrosse
mountain climbing, running
rope skipping
rowing machine
rowing / canoeing for competition
skiing (cross country, downhill, water)
snow shoeing
soccer
stair climbing
squash
swimming laps
tennis (singles)

Muscle Strength and Endurance

calisthenic
hand weights
physical therapy with weights
push-ups
sit-ups
weight-lifting

Heavy Housework

carrying wood
mopping floors
moving furniture
scrubbing floors
sweeping
vacuuming
washing walls
washing windows
washing cars

APPENDIX B:
PASE CODING EXAMPLES

The following examples are provided as guidelines regarding the administration and coding of the PASE.

QUESTION 1

Example: Respondent watches the news every day for one hour. On Tuesday, the respondent plays bingo for three hours. Also, the respondent attends meetings twice a week. One meeting lasts one hour, and the other meeting lasts two hours.

Since the respondent watches TV every day, the interviewer would code sitting activities as often (5-7 days). During the week, the respondent reported 13 hours of sitting (7 hours of TV watching, 3 hours of Bingo, and 3 hours of meeting). Dividing the total hours/week (13) by the days engaged in sitting activities per week (7) results in hours per day engaged in sitting activities (1.9 hours; 1 but less than 2 hours).

Visiting with others, sewing, paperwork, playing musical instruments, playing cards, and/or bingo are considered sitting activities.

QUESTION 2

Example: The respondent walks 30 minutes to 1.5 hours per day.

The average time spent walking was 1 hour. One but less than 2 hours per day is coded for walking.

Example: Three times a week, the respondent walks 3-4 times a day for 15 minutes.

Coding. Throughout the PASE, the number of days rather than the number of occasions is coded. Therefore, the respondent walked sometimes (3-4 days). The respondent averaged 52.5 minutes of walking (3.5 times x 15 minutes) on those days, which is coded as less than one hour of walking outside the home or yard.

Any leisure time, household or work related activity that involves walking is coded entirely under the appropriate activity category (light, moderate, or strenuous sport and recreation, muscle strength and endurance, or work-

related). Hence, walking as part of golf would be coded only as moderate sport and recreation (Question 4) and not as walking (Question 2).

Walking within the respondent's yard is excluded from the question. Treadmill walking should be included under Question 2.

QUESTION 3

Example: The respondent plays golf 4 days per week for 4 hours/day. Three days a week, the golfer uses a power cart. One day a week the golfer walks the course either pulling a cart, carrying the clubs, or the caddy carries the clubs.

Only golf with the power cart would be coded under light sport and recreation. Specifically, the respondent golfed with a cart sometimes (3-4 days/week) for 2-4 hours/day. Golfing without a cart would be marked under moderate sport and recreation as seldom (1-2 days) for 2-4 hours per day. Putting or hitting golf balls at a driving range are coded for light sport and recreation.

Stretching is not coded under and activity category in the PASE.

QUESTION 4

Gardening and lawn work are not coded under leisure time activities. Gardening and lawn work are considered household activities. Question 9B addresses lawn work, and Question 9C pertains to gardening.

QUESTION 5

Example: The respondent swims laps but considers the activity light rather than strenuous sport and recreation.

Swimming laps is coded a strenuous sport and recreational activity regardless of the respondent's assessment of the activity's intensity. Leisure time activities are preassigned activity categories as listed in Appendix A.

Example: The respondent participates in a one-hour aerobics class, 3 days per week. The class consists of 20 minutes of stretching, 20 minutes of hand weights of calisthenics, and 20 minutes of aerobic dance.

Coding. The aerobics class would be coded under two categories. The 20 minutes of aerobic dance would be coded under strenuous activities, and the 20 minutes of calisthenics would be coded under muscle strength and endurance. The 20 minutes of stretching would not be coded under any activity category. Under strenuous activities, the interviewer would list aerobics and circle less than 1 hour/day for 3-4 days per week. Likewise, aerobics would be listed under muscle strength and endurance for less than 1 hour/day for 3-4 days per week.
Climbing stairs as part of an exercise regimen is coded under strenuous sport and recreation. However, stair climbing as part of daily activities is not coded in the PASE.

QUESTION 6

Strenuous work activity, such as moving furniture, is not included in this question. Only activities that are done specifically to increase muscular strength and endurance are used in Question 6.

QUESTION 7

Drying dishes, clothes washing, ironing, hanging up laundry, taking out the garbage, and preparing meals are considered light housework. (See Appendix A.)

QUESTION 8

See Appendix A for applicable activities.

QUESTION 9A

Home repair includes home improvement and maintenance projects such as painting, plumbing, and carpentry.

QUESTION 9B

Snow removal (sweeping snow, shoveling snow or using a snowblower) is considered to be lawn work or yard care. Lawn mowing is counted as lawn work regardless of the type of mower (riding, power, or push) used.

Stacking wood as a household chore is considered to be heavy housework (Question 8); chopping wood outdoors should be coded under Question 9B.

QUESTION 9C

Example: Respondent does outdoor gardening in season. In February, the respondent has not started the garden yet.

Outdoor gardening is coded "no". Only activities performed during the past seven days are coded.

QUESTION 9D

Dependency is defined as a person requiring assistance with activities of daily living (food preparation, personal hygiene, household cleaning). Division of labor within a household (i.e. meal preparation, laundry, yardwork) is not considered dependency.

Babysitting is included in Question 9D. Babysitting is not included in Question 10 as a work-related activity.

Pet care is not considered part of Question 9D.

QUESTION 10

Only work performed during the past 7 days is coded.

Example: The respondent works half the time sitting or standing with some walking, and the other half of the time walking, with some handling of materials.

Higher rather than lower activity levels are coded if the respondent indicates two categories of physical activity required on the job or volunteer work.

Respondents should be encouraged to give their best estimate of the number of hours they worked during the previous seven days. However, if a range of hours is reported (e.g. 15-20 hours), use the midpoint of the range as an estimate.

ECG Set Up and Lead Placement

1. Ask the participant to lie supine on the examination table.

2. Inform them you will be performing an ECG and read the following script:

   An ECG is made up of waves showing the electrical activity in different parts of the heart. In order to get an accurate test please try to lie still. The test takes approximately 10 minutes.

3. Tell the participant you will be placing electrodes on their arms, legs, and chest. Inform them you will be cleaning those areas with Tens Cote Cleaner as well as making marks on their chest with a cosmetic pencil.

4. If he/she is known to be allergic to alcohol, prepare the areas of electrode placement by rubbing with water and drying with a washcloth. If allergies are denied, prepare areas V1, V2-V6, RA, RL, LA, LL, by wiping with a Tens Cote Cleaner. Let dry.

5. **V1:** The first intercostal space is palpated just below the clavicle. Count down and identify the 4th intercostal space just below the fourth rib. **Point V1** is just to the right of the sternum in the ***fourth*** intercostal space. Make a small line with a marking pencil here to show where the ECG lead should be placed.

6. **V2:** Should be at the same level as **Point V1** and immediately to the left of the sternum. Make a small line with a marking pencil to show where the ECG lead should be placed.

7. To locate the horizontal reference level for electrodes **(Point E)**, starting from **V2**, locate the **fifth** intercostal space. Move your finger in the **5th** intercostal space laterally to where the midclavicular (center of the chest where you feel a bend in the clavicle) line intersects the **fifth** intercostal space. Make a horizontal line at this point.

   Mark the exact transverse (horizontal) level at this spot with the midsternal line. It should be about one inch (1") below **V1** and **V2** placements.

8. **V6:** Move the participant's elbow laterally away from the body. Mark the midaxillary line in the exact vertical center plane of the thorax down to the intersection of the horizontal plane marked by the location of **E**. This is the exact location of **V6**. (***NOTE:*** It is a common mistake to locate the midaxillary line too far anteriorly, toward the **V5** location).

9. **V4:** Place the # arm of the Heart Square firmly across the lower sternum at the level of **Point E** (as you face the participant, the writing on the Heart Square will

appear upside down and backwards). Adjust the **E** and **V6** arms of the Heart Square so they are both perpendicular to the long axis of the thoracic spine at the level of the **E** position. The **E** arm should be exactly horizontal. If the participant is lying flat, the **V6** arm should be exactly vertical.

Slide the **V6** arm so the **0** point (the *arrow* labeled **V6**) is at the marked location for **V6**. Double check that the **E** arm is still in the correct spot.

V4: On the **V6** arm (the slide), find the number corresponding to the **E** measurement. Following the corresponding 45 degree line to the surface (e.g. 16) and mark the location following the inside of the square. Place electrodes on ***TOP*** of the breast.

The participant may now lower the left arm in a more comfortable position.

10. **V3:** Exactly halfway between **V2** and **V4**.

11. **V5:** Exactly halfway between **V4** and **V6**.

12. If he/she is known to be allergic to alcohol wipes, prepare the areas of electrode placement by rubbing with water and drying with a washcloth. If allergies are denied, prepare the areas by wiping with an alcohol wipe and drying with a washcloth.

NOTE: Place the electrodes on the participant and hook up the leads before entering the data in the ECG machine. This will allow ample time for the participant to relax and the machine interference to smooth out.

13. Attach limb leads in the following order: right arm (RA), right leg (RL), left arm (LA), left leg (LL) parallel to the limb with tabs facing toward the heart. This will avoid lead reversal.

14. The body of the electrode is placed centrally at the pencil mark with the tab extending downward. Precordial electrodes are attached in the following order: V1, V2, V3, V4, V5, V6. Recheck all leads for proper placement.

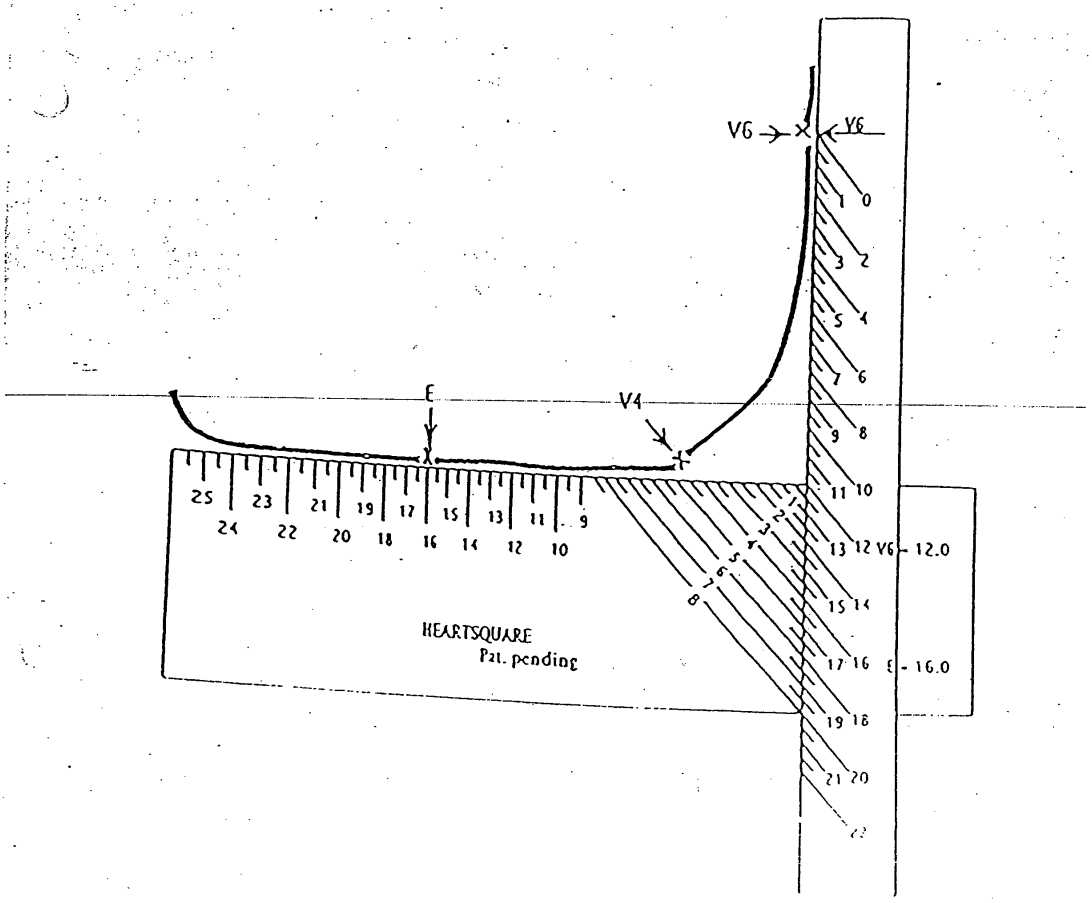
15. Ask the participant to lie still and relax. In the computer, enter the participants Name, ID, Age, Height, Weight, and Gender. Enter the Exam Cycle, Location (1=clinic), and your Tech ID.

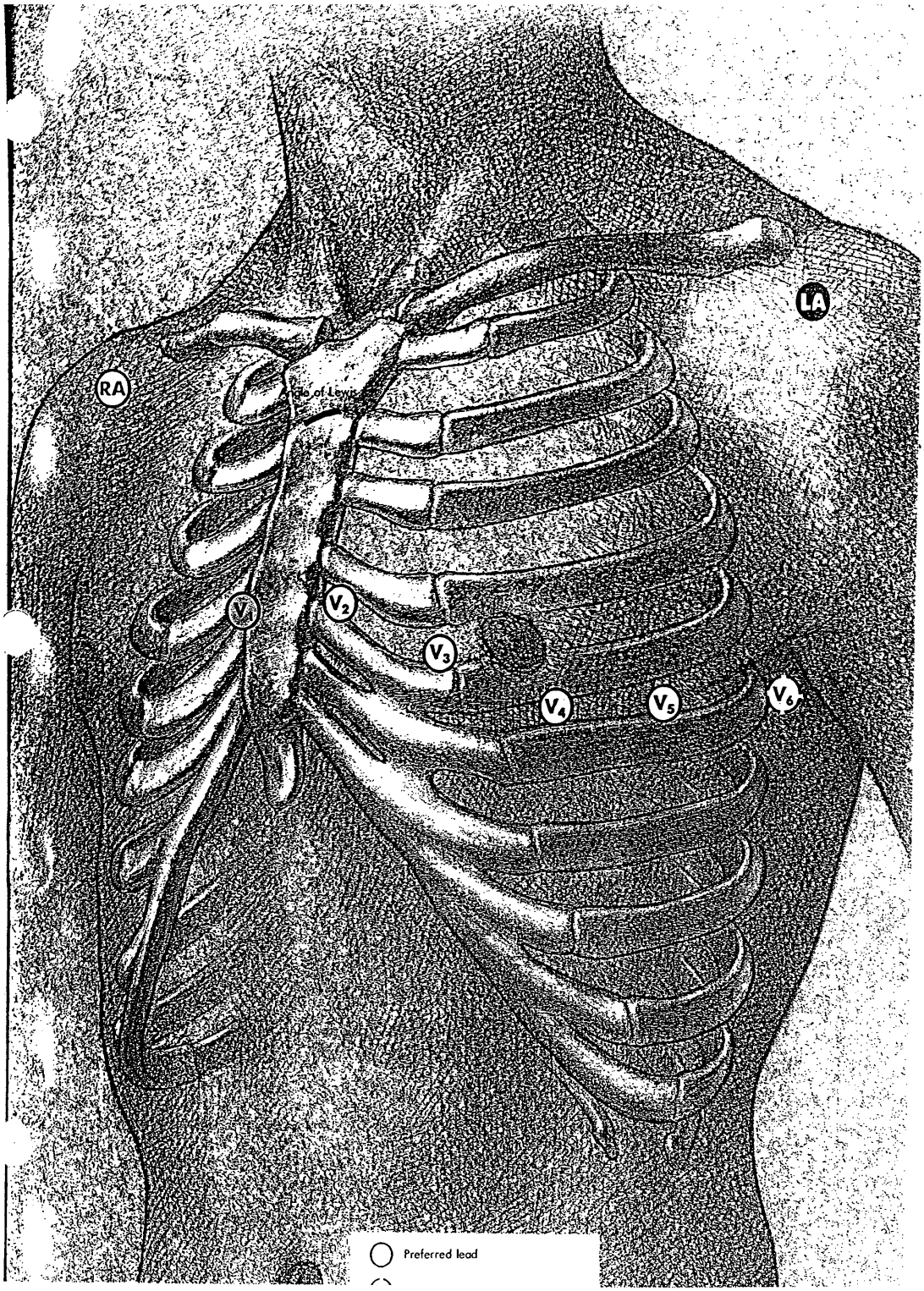
16. The ECG is printed and reviewed for errors. If ECG needs to be run at **5 mmHg** because of high voltage (if the standard **10 mmHg** is beyond the lines of the ECG paper), highlight (yellow or orange highlighter) the **5 mmHg** on the bottom of the

printed ECG. On the top margin of the tracing write " *1/2* ***STANDARD***" using a bold magic marker.

17. Leads are checked again for proper placement and disconnected. Electrodes are carefully removed.

18. After each use, wash the Heart Square gently with soap and water (1 part detergent to at least 20 parts water, approximately 3 drops of detergent to one cup of water) and gently wipe dry with a soft cloth.


V6
V6
E
V4
25
24
23
22
21
20
19
18
17
16
15
14
13
12
11
10
9
HEARTSQUARE
Pat. pending
V6 - 12.0
E - 16.0


RA
LA
Angle of Lewis
V1
V2
V3
V4
V5
V6
Preferred lead

Equipment for ECG

- ECG Machines: GE MAC5500 (3)

  Marquette Electronics

  100 Marquette Drive

  Jupiter, FL 33468-9100

  Sales Rep: Kevin Manning

  781-439-5969 (cell)

  Kevin.manning@ge.com

- ECG Carts
- MUSE
- Heart Square
- Tens Cote
- Cosmetic pencil

Date: _____ **Tech ID#_____**

Supervisor:_____ **Participant_____**

ECG Supervisor Checklist

Check that each procedure is carried out correctly. Check yes if correct or no if incorrect. Provide an explanation of the incorrect item. Items are presented in the sequence of the examination procedure, but may require confirmation before or after the exam.

Yes	No	ECG Procedures
		Participant is informed that ECG is going to be done. Procedure is explained. Participant is asked to lie on bed, get comfortable.
		Tech establishes a rapport with participant so participant is at ease with procedure. Answers any questions participant may have.
		Electrode location V2 is located in the 4th intercostals space at the left sternal border, a mark is made with pencil.
		V1 is found at the same level as V2 but at the right sternal border, a mark is made.
		The E point is located at the intersection of the 5th intercostal space and the mid-clavicular line, a mark is made.
		A line is drawn at mid axillary in exact vertical center plane of the thorax.
		V6 is located in the mid axilla at the same level as the E point. (The heart square should be firmly placed on the body and kept on a horizontal plane from the E point to the mid-axillary point).
		The difference between the E measurement and V6 measurement is calculated.
		The difference from the above calculation is located in the heart square and V4 is located on the chest, a mark is made.
		V3 is located midway between V2 and V4, a mark is made.
		V5 is located midway between V4 and V6, a mark is made
		Tens Cote wipe is used to clean each area, RA, RL, LA, LL, V1 – V6
		RA electrode is located on the upper (dorsal) surface of right forearm, placed with tab extending away from body.
		RL electrode is located on the inside surface of the right lower leg, placed with tab extending away from body.
		LA electrode is located on the upper (dorsal) surface of left forearm, placed with tab extending away from body.
		LL electrode is located on the inside surface left lower leg, placed with tab extending away from body.
		Chest Electrodes are placed at V1, V2, V3, V4, V5, V6 with the body of the electrode placed centrally on each pencil

		measurement, tab extending down.
Yes	**No**	**ECG Procedures (cont'd)**
		Leads are connected to electrodes in the following order: RA, RL, LA, LL, V1 – V6
		All leads are rechecked for proper placement
		The participant's identifying information is typed into the MAC.
		Participant is requested to relax and lie quietly while ECG recording is in process.
		When tracing appears acceptable, the ECG is printed and reviewed for errors
		All leads are rechecked for proper placement and then disconnected and electrodes gently removed
		2 copies of the ECG is printed and stamped with the correct exam number.

Comments/Corrections:
Supervisor:
Date:

Observed Physical Performance

A. Overview:

An objective performance measure of physical functioning is an assessment instrument in which an individual is asked to perform a specific task and is evaluated in an objective, standardized manner using predetermined criteria, which may include counting of repetitions or timing of the activity as appropriate. Two theoretical models of the pathway from disease to disability have been developed. The first comes from the World Health Organization and goes from disease to impairment to disability, to handicapped. The second, which is being used more now by geriatricians and aging researchers, progresses from disease, to impairment, to functional limitations to disability.

B. Methods:

During all tests, participant safety is paramount. Participants who do not feel safe or who are unable to perform a test should not be pressed. All procedures should be clearly demonstrated to the participant prior to performing any test and the participant should be queried to ensure that they understand the instructions. If it is obvious that the participant has not understood the directions, reread the standard instructions. You will be demonstrating each maneuver. Someone who may not completely understand the verbal instructions may still be able to perform the test following the demonstration.

C. Equipment:

1. Laptop
2. Measured 4 meter walking course (3-4 meters for offsite exams)- Masking Tape
3. Stopwatch
4. JAMAR Dynamometer
5. Straight back chair with arm

D. A note on encouragement:

If a participant expresses doubt as to whether he or she can perform the task, ask the participant whether they would like to try. If they say yes, proceed with the task but if they say no, honor the participant's choice to decline the testing.

E. Introductory script:

We are going to try to do different physical activities.

I will first explain what I would like you to do, then I will demonstrate it for you and then I will ask you to try it for me.

F. Performance Measures:

1. Hand Grip Strength Test

2. Measured Walks

JAMAR Hand Grip Strength Test

1. *Script*: ***This instrument will measure your grip strength. The instrument is a little heavy, so be careful. When I tell you, I want you to squeeze the instrument as hard as you can. Do not expect the handle to move very much.***

6. Participant is seated in chair with feet flat on the ground and forearms resting on chair arms, elbows are at about a 90 degree angle.

7. Participant should hold JAMAR in upright position and the wrist is in neutral position. The hand grip can be adjusted for those with larger hands.

8. The examiner should be close enough to the participant to be able to catch the JAMAR in case it is dropped.

9. Make sure that red peak-hold needle is set to zero.

10. Tell participant to squeeze as hard as s/he can, and squeeze until you tell s/he to stop.

11. Say "Ready, Squeeze" once. Have participant hold squeeze for a 3 to 5-1000 second count.

12. Take back JAMAR, hold at eye level, about a foot from your eyes, and record reading on the kilogram scale. If directly in the middle of the scale then the reading is the odd number between the two even hash marks; otherwise record as the closest hash mark.

7. Repeat steps until three measurements are recorded with the right hand.

8. Repeat steps for three trials with the left hand.

9. If only one hand is completed then test is still coded as completed.

HAND GRIP SCRIPT

"I want you to squeeze this **AS HARD AS YOU CAN** until I tell you to stop.

You won't feel this moving (point to handle) but it is measuring.

We would like you to do this 3 times in each hand.

Is this OK with you?"

"Please sit up straight, feet flat on the floor and rest your arm on the chair arm."

(If ppt is short, have them move forward on the chair a little so balls of feet are on floor. For men, make sure grip is not resting on their leg)

(Give hand grip to ppt after zeroing it)

"Don't squeeze yet" (make sure you are zeroed)

SAY: "Squeeze, Squeeze, Squeeze" and then count 1-1000, 2-1000, 3-1000.

"Good" or "Stop"

"Good job!"

(Zero grip). "Let's do it again."

(and repeat above instructions)

Measured Walks

Description:

The participant will first observe while **the examiner demonstrates** how to walk the measured course at a normal pace. The participant will then be asked to walk the measured 4 meter course at their normal walking pace. Next, he or she will repeat this normal pace while being timed twice. The examiner will then demonstrate the fast pace walk and the participant will be asked to walk the course at a fast pace while being timed.

In Clinic only, the participant must be wearing socks or shoes they cannot be barefoot. If Offsite, a 3 meter course may be used if a 4 meter course is not available (this will be marked on the data sheet).

A cane or walker may be used during the walk, but if participants with such devices can walk short distances without them, they should be encouraged to do so. Many people with assistive devices use them only when they walk outdoors or for long distances indoors. Doing the test without the device provides a much more accurate assessment of the functional limitation of the participant. Ask the participant if he/she ever walks at home without the device. Then ask the participant if s/he thinks he/she can walk a short distance for the test. Participants who normally use assistive devices should be watched particularly closely during the test to prevent falling.

If a walking aid is used, this will be recorded:

Coding

0 = No aid	**2** = Walker	**4** = Other
1 = Cane	**9** = Unknown	

Training Note: we do not do timed walks for participant in a wheelchair.

Methods:

The walking course should be unobstructed and include at least an extra one-half meter on each end. You will need a measuring tape to measure the distance of the walking course and masking tape to mark the starting and finish lines. An X should be made at the end of the course approximately one foot after the finish line.

Procedures:

1. Have the participant line their toes up with the starting line.

2. Have the stop watch set at zero and say "*Ready, begin*".

3. Start timing with the stopwatch when you see the participant start to move. Stop timing when the participant breaks the plane.

4. Record the stop watch time in hundredths of seconds

5. If the test needs to be repeated due to participant or staff error, start over.

1. Walk #1:

Script: Now I am going to observe how you normally walk, if you use a cane or other walking aid and would be more comfortable with it, you may use it.

This is our walking course. I want you to walk to the other end of the course at your usual speed, just as if you were walking down the street. Keep walking until I tell you to stop. Please ignore the tape on the floor.

Please watch while I demonstrate. After the demonstrations ask, do you think this will be safe? If they say yes, proceed. If not, abort test.

Have the participant line up his or her toes behind the line on the floor. Start the laser box and start timing with the stopwatch when you see the participant start to move and stop timing when the participant breaks the plane at the end of the course. Record the stopwatch time.

2. Walk #2:

Script: Now I want you to repeat the walk. Remember to walk at your usual pace, and keep walking until I tell you to stop.

Ready? Begin.

3. Walk #3:

Script: Now I want you to repeat the walk again, but this time, I would like you to walk at a rapid pace, as fast as you can. Make sure you continue walking until I tell you to stop.

Please watch while I demonstrate. Do you think this will be safe for you to do?

Ready? Begin.

Coding:

For each walk, the following questions will be answered:

1. Walk time
2. Course in Meters (3 or 4) for Offsite visits only
3. Walking Aid used (0=No aid, 1= Cane, 2= Walker, 3=Other, 9=Unknown)
4. Check if this test not completed or attempted
5. If not attempted or completed, why not?
   1=Physical Limitation
   2=Refused
   3=Other_____write in
   9=Unknown

Information on Observed Physical Performance found in this section was obtained through:
Guralnik MD, PhD, Jack. Assessing Physical Performance in the Older Patient: An overview of the Short Physical Performance Battery (SPPB). CD-ROM. 2003
Timed Laser Walk(s) were obtained through: ***FHS Laser Walk Test Manual 6/23/06***
Handgrip protocol was obtained through*:* ***Performance-Based Measures of Physical Function for High-Function Population. Curb, David et al.***

Date: _____ Tech ID#_____ Quarter: I, II, III, IV (circle one)
Supervisor: Emily Manders Participant Label_____

Observed Physical Performance Measures
Supervisor Checklist

Check that each procedure is carried out correctly. Check yes if correct or no if incorrect. Provide an explanation of the incorrect item. Items are presented in the sequence of the examination procedure, but may require confirmation before or after the exam.

Yes	No	JAMAR Hand Grip Strength Test
		Introductory script: ***This instrument will measure your grip strength. The instrument is a little heavy, so be careful. When I tell you, I want you to squeeze the instrument as hard as you can. Do not expect the handle to move very much.***
		Participant is seated in chair with arms, forearm resting on chair arm, elbow at about a 90 degree angle.
		Participant should hold JAMAR in upright position, wrist in neutral position, JAMAR facing the technician.
		Make sure that red peak-hold needle is set to zero.
		Tell participant to squeeze as hard as s/he can, and squeeze until you tell s/he to stop. Hold squeeze for a 3 to 5-1000 second count.
		Take back JAMAR, hold at eye level at about a foot from your eyes and record reading on the kilogram scale. If directly in the middle of the scale then the reading is the odd number between the two even hash marks; otherwise record as the closest hash mark.
		Repeat steps until three measurements are recorded with the right hand.
		Repeat steps for three trials with the left hand.

Timed Walk(s)

Yes	No	Instructions for Technician: Walk One
		Now I am going to observe how you normally walk, if you use a cane or other walking aid and would be more comfortable with it, you may use it.
		This is our walking course. I want you to walk to the other end of the course at your usual speed, just as if you were walking down the street. Walk all the way *past the other end of the tape before you stop. Do you think this would be safe?*
		If participant says that it would not be safe indicate this on the data sheet and abort walks.
		Please watch while I demonstrate. When I want you to start, I will say "Ready, begin."
		Have the participant line up his or her toes behind the line on the floor. Start timing when you say, "begin" and stop timing when the participant breaks the plane of the line at the end of the course. Record the time on data sheet.

Date: _____ Tech ID#_____ Quarter: I, II, III, IV (circle one)
Supervisor: Emily Manders Participant Label_____

Yes	No	Instructions for Technician: Walk Two
		Now I want you to repeat the walk. Remember to walk at your usual pace, and all the way past the other end of the course. *Ready? Begin.*

Yes	No	Instructions for Technician: Walk Three
		Now I want you to repeat the walk again, but this time, I would like you to walk at a rapid pace, as fast as you can. Make sure you go all the way past the other end of the course. *Please watch while I demonstrate.* *Ready? Begin.*
		For each walk, the following questions will be answered: *Was this test completed?* **Coding** **0** = No **1** = Yes **8** = Not attempted **9** = Unknown *If the test was not attempted or completed, why not?* **Coding** **1** = Physical limitation **2** = Refused **3** = Other (write in) ***9*** = Unknown
		Walk time for each walk is recorded.

Date: _____ Tech ID#_____ Quarter: I, II, III, IV (circle one)
Supervisor: Emily Manders Participant Label_____

		For each walk, the following questions will be answered: *Was this test completed?* **Coding** **0** = No **1** = Yes **8** = Not attempted **9** = Unknown *If the test was not attempted or completed, why not?* **Coding** **1** = Physical limitation **2** = Refused **3** = Other (write in) ***9*** = Unknown
		Walk time for each walk is recorded.

Yes	**No**	**Deviations**
		Did the tech perform any minor deviations?
		Did the tech perform any major deviations?
Comments/Corrections/Deviations:		
Supervisor Initials:		
Date:		

Seated Blood Pressure

A. Equipment:

1. One standard Litman stethoscope tubing and earpieces with bell: Classic II 3M

2. One standard mercury column sphygmomanometer: Baumanometer

3. BP cuffs in four sizes (all Latex free)

   Thigh adult cuff
   Large adult cuff
   Regular adult cuff
   Pediatric cuff

B. Blood Pressure Cuff Placement:

1. Bare participant's left arm to above the point of the shoulder.

2. Determine correct cuff size using guidelines inside the cuff.

3. Palpate the brachial artery.

4. With participant seated, place the appropriate cuff around the upper left arm. The midpoint of the length of the bladder should lie over the brachial artery. Each cuff has an artery marker. The mid-height of the cuff should be at heart level.

5. Place the lower edge of the cuff, with its tubing connections, about one inch (1") above the natural crease across the inner aspect of the elbow.

6. Wrap the cuff snugly about the arm, with the palm of the participant's hand turned upward.

7. If the subject has had a left-sided mastectomy, the right arm may be used for blood pressure measurement. If right arm is used, note it in the comment section.

C. Determination of Maximal Inflation Level

For each participant, determine the maximal inflation level, or the pressure to which the cuff is to be inflated for blood pressure measurement. This assures

that the cuff pressure at the start of the reading exceeds the systolic blood pressure and thus allows the first Kortokoff sound to be heard.

1. Attach the cuff tubing to the sphygmomanometer.

2. Palpate the radial pulse.

3. Inflate the cuff rapidly until the radial pulse is no longer felt (palpated systolic pressure) by inflating rapidly to 70 mmHg, then inflating by 10mmHg increments.

4. Deflate the cuff quickly and completely.

5. The maximal inflation level is 30 mmHg **above** the palpated systolic pressure.

D. Guidelines for Accurate Blood Pressure Readings:

1. The participant should be in a seated position for at least 5 minutes before the blood pressure is measured with both feet remaining flat on the floor.

2. All readings are made to the nearest even digit.

3. Any reading which appears to fall exactly between marking on the mercury column should be read to the next higher marking (i.e. 2, 4, 6, 8, or 0).

4. All readings are made to the top of the meniscus, the rounded surface of the mercury column.

5. When the pressure is released quickly from a high level, a vacuum is formed above the mercury and the meniscus is distorted. Allow a few moments for it to reappear before reading the manometer.

For offsite Blood Pressures: Check that the needle is at the zero mark at the start and the end of the measurement. Place the manometer in direct line of sight with the eye on a line perpendicular to the center of the face of the gauge.

E. Blood Pressure Readings:

1. Following any previous inflation, wait at least 30 seconds after the cuff has completely deflated.

2. By closing the thumb valve and squeezing the bulb, inflate the cuff at a rapid but smooth continuous rate to the maximal inflation level (30 mmHg above palpated systolic pressure).

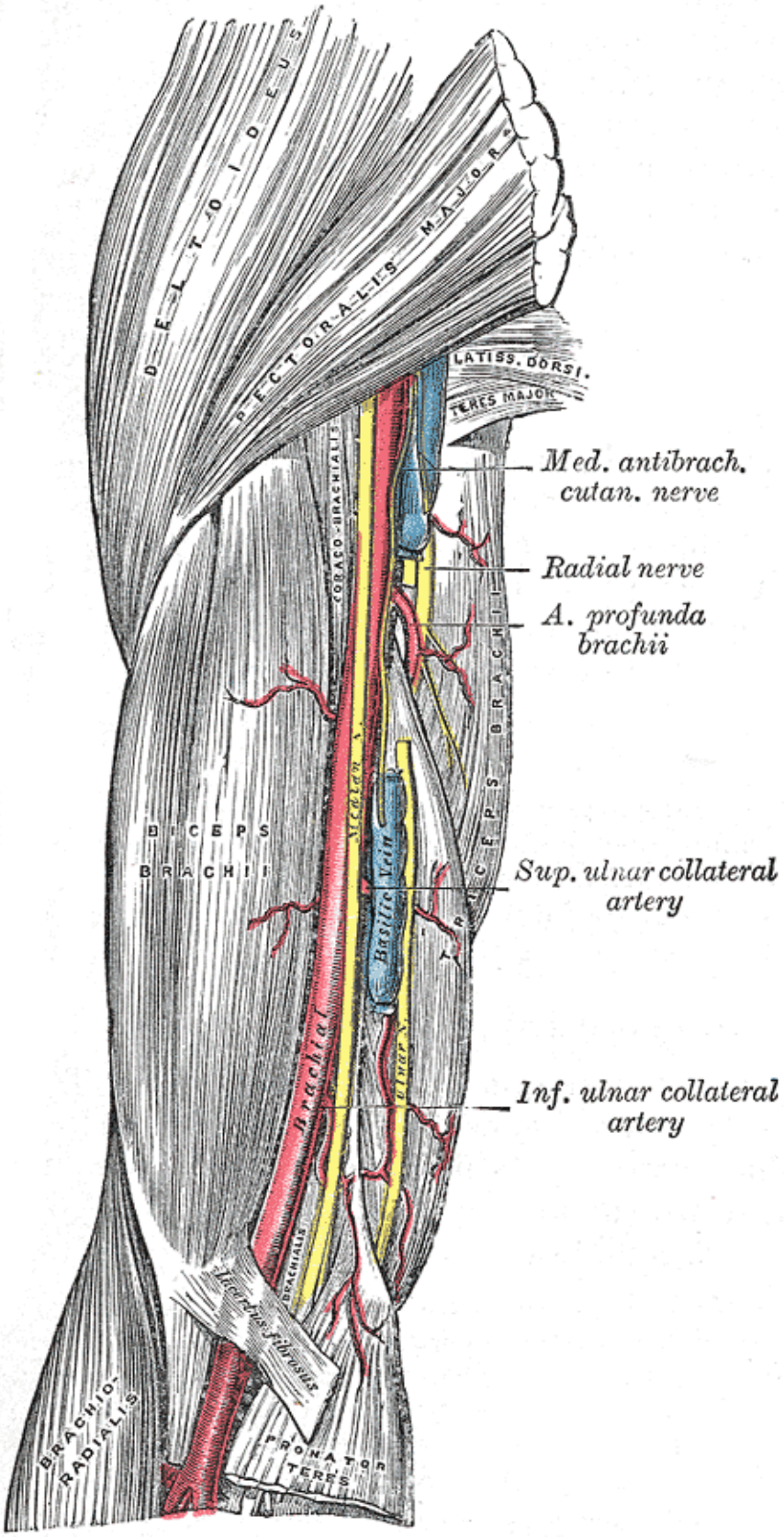
3. The examiner's eyes should be level with the mid-range of the manometer scale and focused at the level to which the pressure will be raised.

4. Open the thumb valve slightly. Allow the cuff to deflate, maintaining a constant rate of deflation at approximately 2 mmHg per second.

5. Using the bell of the stethoscope, listen throughout the entire range of deflation, from the maximum pressure past the systolic reading (the pressure where the FIRST regular sound is heard), until 10 mmHg BELOW the level of the diastolic reading (that is, 10 mmHg below the level at which the LAST regular sound is heard).

6. Deflate the cuff fully by opening the thumb valve.

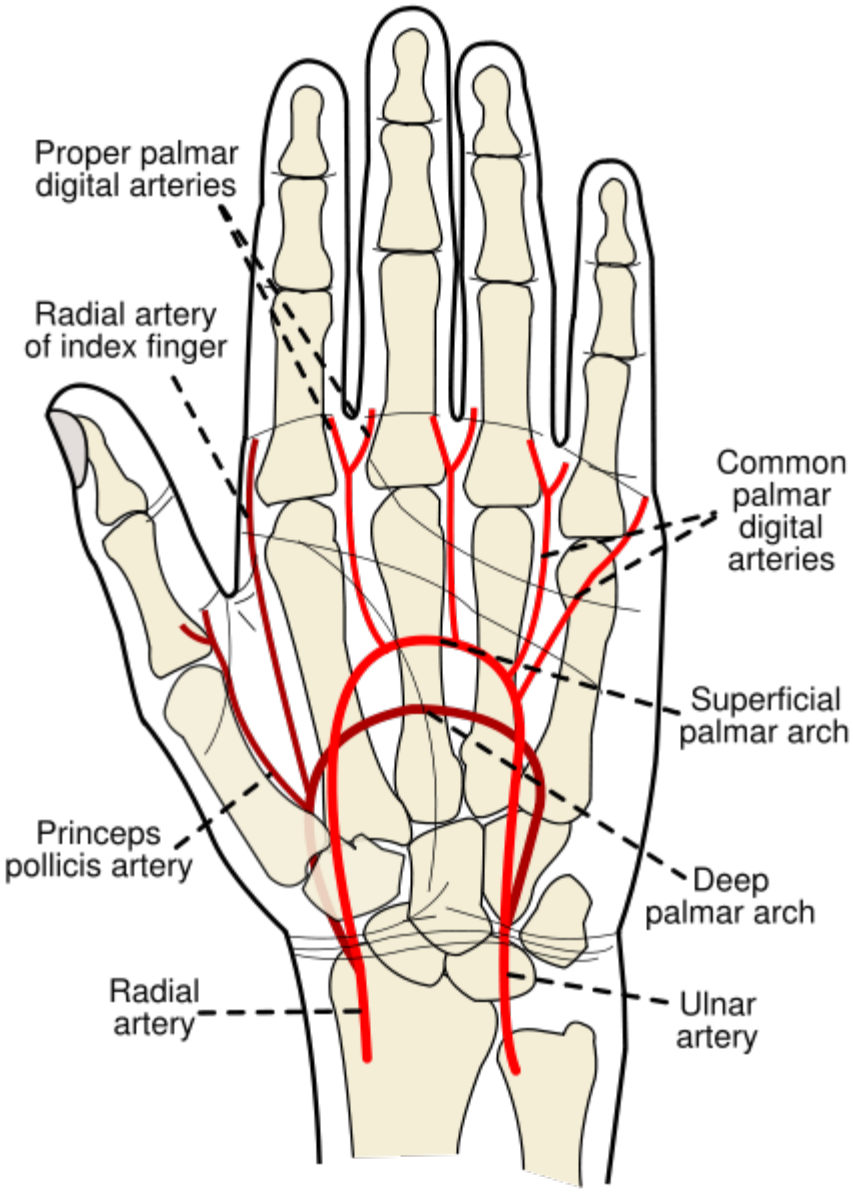
7. Remove the stethoscope. Neatly enter systolic and diastolic readings in the spaces provided on the form.



<u>Brachial Artery</u>:

Located between the biceps and triceps, on the medial side of the elbow.

Radial Artery: Located on the thumb side of the wrist.



MD BP CERTIFICATION

MD	Cerification Date		Certified by	Recertification Date	Recert by

X = not in clinic anymore

Record Of In-Research Center Medical Encounter

(to be filed in chart)

Participant's ID#: _____ Participant's Name:_____

Date of Incident: ____/____/____

Description of Incident:

_____

_____

_____

_____

_____

_____

_____

_____

Physician:_____

Follow-Up (if any)

Date of Follow-Up: ____/____/___

_____

_____

_____

_____

_____

_____

_____

Physician/Staff:_____

Record Of Telephone Encounter

(to be filed in chart)

Participant's ID#: _____ Participant's Name: _____

Date of Incident: ____/____/____

Person Contacted:_____

_____

Regarding:_____

_____

_____

_____

_____

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_____

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_____

_____

_____

_____

Contact Made By:_____

_____

_____

Neurology Referral Form

ID#:_____ Name:_____
Date:____/____/____ Person Making Referral:_____

Source of Referral:_____

1 = Hospital Admission
2 = Biennial Exam
3 = Offspring Exam
4 = Family
5 = Medical Records
6 = Other (Please specify)
7 = Review

Reason for Referral:_____
_____
Reason for Hospitalization (if applicable):_____
_____

Living Situation (if applicable): _____

1 = Own Home
2 = Elderly House
3 = Hospital
4 =Relative's Home
5 = Nursing Home
6 = Other

DISPOSITION (OFFICE USE)

Date Opened: ____/____/____
Date Closed: ____/____/____

1. To be scheduled for Neuro Clinic
2. Seen in Neuro Clinic: ____/____/____
3. Medical Records to be Obtained
4. Medical Records Complete: ____/____/____
5. Review Status:_____
   1 = Reviewed
   2 = Awaiting review
   3 = No review to be done
6. Enrolled Case in Stroke Study:_____
   1 = No
   2 = Yes
   Date:____/____/____
7. Reasons Not Seen:_____
   1 = N/A
   2 = Refused
   3 = Deceased
   4 = Out of state
8. Previously Seen:_____
   1 = Stroke
   2 = Dementia

Stroke Tracking Referral Form
The Framingham Study

* Please complete the upper portion of this form if you identify a new neurological event.

ID#:_____ Name:_____
Date Opened: ____/____/____
Date of Event: ____/____/____ Date Type:____ (0=Exact, 1=Approximate)
Source of Referral:_____

1 = Hospital Admission
2 = Biennial Exam
3 = Offspring Exam
4 = Family
5 = Medical Records
6 = Review
7 = Other (Please specify)

Initials:_____
Reason for Referral:_____
Reason for Hospitalization:_____ (1=Neurology, 2=Other, 8=NA)
Comments:_____
_____
_____

DISPOSITION (FOR TRACKING PERSONNEL TO COMPLETE)

1. Dictation:_____ (0=Awaiting, 1=In)
2. To be Scheduled in Stroke Clinic:_____ (0=No, 1=Yes, 2=Pending)
3. Date Seen in Stroke Clinic:____/____/____
4. Reason Not Seen in Clinic:_____ (1=NA, 2=Refused, 3=Deceased, 4=Out of State)
5. Part of PSIP Follow-Up Protocol:_____ (0=No, 1=Yes, 9=Unknown)
6. Previously Seen:_____ (0=No, 1=Stroke, 2=Dementia, 3=Other)
7. Medical Records needed:_____ (0=No, 1=Yes)
8. Date:____/____/____
9. CT/MRI/MRA to be obtained:_____ (0=No, 1=Yes)
10. Date:____/____/____
11. Review Status:_____ (1=Awaiting Review, 2=Reviewed, 3=Need Info)
12. Date Reviewed:____/____/____
13. Status of Case:_____ (1=Open, 2=Closed)
14. Date:____/____/____
15. Diagnosis:_____
    (1=Stroke, 2=TIA, 3=? TIA, 4=Parkinson's, 5=No CVA, 6=Other Neuro, 7=Migraine, 10=?Stroke, 20=Recurrent TIA, 9=Unknown)

Medical History

The date of the participant's last exam and the date of the participant's last health history update will be in the participant's chart. The medical history taken from the participant is an update from the Heart Study's last contact with the participant (based on the date of the last Health History Update or last examination). The examiner should also refer to the Summary of Findings form in the participant's chart to verify whether a medical encounter is new or has already been identified. This form records the outcome of all Endpoint reviews and therefore documents all cardiovascular disease events adjudicated by the study.

The health status page may have incomplete data on medical encounters. Be sure to clarify any missing information and record it under medical encounters on the first screen of the medical history form.

Medical History Form

1st Examiner Prefix

(0=MD, 1=Tech, for OFFSITE visit)
Note: zero is in as a default, for OFFSITE visits, slash the zero out and write in 1 for Tech

Hospitalization in interim

A hospitalization is considered an overnight stay.
If the participant was in the Emergency Room (E.R.) and then admitted, the event would be considered only for hospitalization and not as E.R. visit.

E.R. visit in interim

An emergency room visit is when the person is both admitted to and discharged from the emergency room the same day.

Day surgery in interim

Day surgery is a surgical procedure performed on an out-patient basis either in an ambulatory surgery department of a hospital or in a physician's office.
The person is in and out the same day.

Major illness with visit to the doctor in interim

Illness with visit to physician is defined as a visit outside of a regular check-up. It can be further clarified by defining it as a visit to the doctor for a specific reason. It is imperative that the reason for the visit be documented.

Check-up in interim by doctor

A check-up is considered to be a routine visit.

Details of all hospitalizations, ER visits, day surgery, and physician visits must be provided as follows:

A. Medical Encounter
Write the details about the medical event. If the participant cannot provide a "medical condition", symptoms leading to the medical encounter should be listed (for example, chest pain, shortness of breath).

B. Month/Year
Record the date of the medical encounter. People often cannot recall the exact month or even the year. Trying to couple the event with a season or holiday sometimes helps.

C. Site of the hospital or office
The hospital and the city and state are most important.

D. Doctor
Record the name of the physician seen. If the participant sees a physician's assistant or a nurse practitioner in the physician's office, obtain both names.

Note: If FHS needs outside hospital records, please obtain details: mo/yr, hospital site.

Medical History – Prescription and Non-Prescription Medication

At FHS and at Offsite visits, the participant is asked to show the FHS staff his/her medication bottles including over-the counter preparations. The FHS staff takes a picture of the medication on the computer or tablet. In the case of a nursing home visit, the technician should record the medications from the participant's medication orders in their nursing home chart.

Take a picture of the name of the medication, the strength including units, and the total number of doses per day/week/month. Include pills, skin patches, eye drops, creams, salves, injections. Include herbal, alternative, and soy-based preparations.

Make sure the medication name, strength, number per day/week/month, and if taken PRN is shown clearly on the picture.

*****List ONLY medications taken regularly in the past month/ongoing medications*****

Medical History

The physician/NP will obtain an interim medical history using the Exam 10 RedCap form. The questions should be asked exactly as written on the form and the participant's response recorded according to the response choices provided on the form. In addition a comment area is provided on the form to record a narrative account of cardiovascular symptoms including chest pain, shortness of breath, syncope, exertional leg discomfort and cerebrovascular symptoms. It is critical that a narrative be provided to clarify the symptoms for investigators adjudicating events in Endpoint Review.

It is also critical to record all health care visits (physician, ER, hospital) the participant has had for the symptom. Outside medical records will be obtained to verify the participant's account of their medical condition.

Additional instructions for obtaining the medical history and properly coding the participant's responses are as follows.

Chest pain (screen MD13)

When the participant states that they have not experienced any chest discomfort, clarify further using the terms *chest pain, chest tightness, chest pressure*.

If the participant states that they never used Nitroglycerin as a way to relieve the discomfort be sure to code as 8= not tried, rather than 0= no relief.

Alcohol Consumption (screen MD09)

Code number of alcoholic beverages as EITHER weekly **OR** monthly as appropriate.

Cerebrovascular, Neurological and Venous Diseases (screen MD15)

It is important to stress that these CVA symptoms are **sudden**, not a gradual progression of a symptom.

1. Sudden Muscular Weakness
   *Since (date of last FHS exam) until today, have you experienced any **sudden** muscular weakness? For example, face drooping or weakness, particularly on one side of your body.*

2. Sudden Speech Difficulty
   *Since (date of last FHS exam) until today, have you experienced any **sudden** difficulty with your speech such as understanding spoken words or trouble speaking?*

3. Sudden Visual Defect
   *Since (date of last FHS exam) until today, have you experienced any **sudden** visual defect?*

4. Sudden Double Vision
Since (date of last FHS exam) until today, have you experienced any double vision?

5. Sudden Loss of Vision in One Eye
*Since (date of last FHS exam) until today, have you experienced any **sudden** loss of vision in one eye, like a shade coming down over your eye?*

6. Sudden Numbness, Tingling
Since (date of last FHS exam) until today, have you experienced any numbness or tingling on one side of your face or one side of your body?

If the participant answers yes, ask is numbness and tingling positional?

CVD Procedures (screen MD17)
The participant is queried regarding CVD procedures since the last Heart Study contact.
If the participant has had more than one procedure of a particular type code only the first procedure and list all other procedures in the comment section.

Clarify the procedure list for the participant as follows:

Heart valvular surgery
Have you had surgery on your heart valves?

Exercise tolerance test
Have you had an exercise stress test or a treadmill test of your heart?

Coronary Arteriogram
This test is an invasive test done in the hospital. An x-ray is taken of your arteries after you receive an injection of a dye that outlines the blood vessels of your heart.

Coronary artery angioplasty/stent/PCI
Angioplasty is a procedure in which a balloon is used to open a narrowed or blocked artery in your heart. (This is also known as Percutaneous Coronary Intervention (PCI)). A stent is a wire mesh tube that is placed in the artery to hold it open. The stent is usually placed in the artery during angioplasty.

Coronary bypass surgery
Have you had bypass surgery also known as CABG (coronary artery bypass grafting)? During bypass surgery the diseased section of your coronary arteries are bypassed with a healthy artery or a vein in order to increase blood flow to your heart muscle.

Permanent pacemaker insertion
Have you had a pacemaker inserted? A pacemaker is used to replace the function of the natural pacemaker in your heart when your heart is beating too slowly. Permanent pacemakers are surgically placed into the chest through a small incision.

AICD
This stands for Automatic Implantable Cardiac Defibrillator (AICD) and is a device that is implanted under the skin of the chest to analyze the rhythm of your heart and discharges an electrical shock if a serious irregularity is detected.

Carotid artery surgery/stent
The carotid artery is located in your neck and carries blood and oxygen to your brain. Carotid artery surgery is a surgical procedure to restore adequate blood flow to your brain. A stent is inserted into the carotid artery to open a narrowed or blocked area of the artery to help maintain an adequate blood flow to the brain.

Thoracic aorta surgery
Have you had surgery on your aorta- the large blood vessel coming from your heart? This surgery is done to repair the aorta for example when there is an aneurysm (a weaknening or bulge in the wall of the aorta) .

Abdominal aorta surgery/stent
Have you had surgery on the large blood vessel in your abdomen (belly) called the aorta? This surgery would be done to repair a problem such as an aneurysm (weakening or bulge in the wall of the artery) or blockage in the aorta.

Femoral or lower extremity surgery/stent/angioplasty
Have you had any surgery to improve the circulation in your legs such as bypass surgery or angioplasty?

Lower extremity amputation
Have you had an amputation of part of your leg or foot?

Other cardiovascular procedures (write in)
Have you had any other tests or procedures on your heart or blood vessels?

ECG Coding for Framingham Heart Study Examinations

Although the computerized ECGs which are recorded in the Research Center include measurements of rate, intervals and axis, it is important that the NP/MD carefully examine the ECG. The heart rate, intervals and QRS angles will be obtained by the Mac 5500.

An important rule to remember: Please ask for help when you are unsure about interpretation of ECGs or our methods of coding**.** Compare to the ECG from the last exam for interim changes. If changes are noted, look for outside ECGs that are more recent to determine whether the change is truly new.

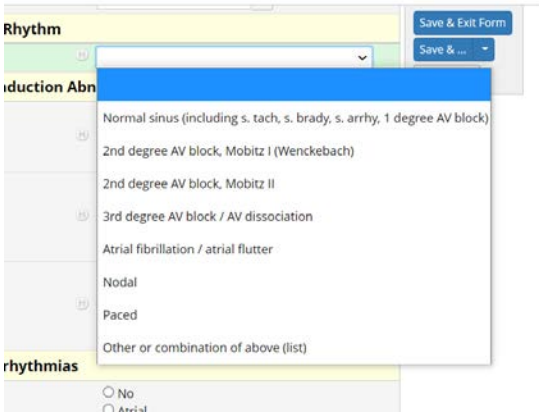
Rhythm

The presence of rhythm disturbances should be made based on examination of the ½ speed rhythm strip which accompanies each ECG. This represents a simultaneous 3 lead recording of the entire 12-lead ECG.

Rhythm - predominant

- Normal sinus (including s. tach, s. brady, s. arrhythmia, 1st degree AV (PR interval ≥ .20 sec [measured in lead II])
- 2nd degree AV block -- some P waves are not conducted:
- 2nd degree AV block, Mobitz I (Wenckebach) (progressive PR prolongation precedes the dropped P wave)
- 2nd degree AV block, Mobitz II (QRS complexes are dropped without prior PR prolongation)
- 3rd degree AV block / AV dissociation (P waves and QRS complexes march out independent of each other)
- Atrial fibrillation / atrial flutter
    - [WPW, APC, and atrial enlargement should be coded as UNKNOWN]
- Nodal (junctional or accelerated junctional rhythm, can occur with AV dissociation or 3rd deg AVB)
- Paced
    - [IV Block, Hemiblock, WPW, MI, T wave changes, RVH, and LVH should be coded as FULLY PACED or Unknown]
    - If pacing is intermittent, code the non-paced beats for MI/LVH/BBB, etc and place a note in the comment section
    - Participant may have pacemaker but ECG may not have any paced beats
    - If V-paced (not A-paced) can code LAE, WPW
    - If V- paced and SR, code as V paced
    - If V-paced and AF, code as a combination: AF and V-paced
- Other or combination of above (list) (specify combination)

    [If dual rhythms and some of rhythm is partially readable for MI- may still CODE for MI]



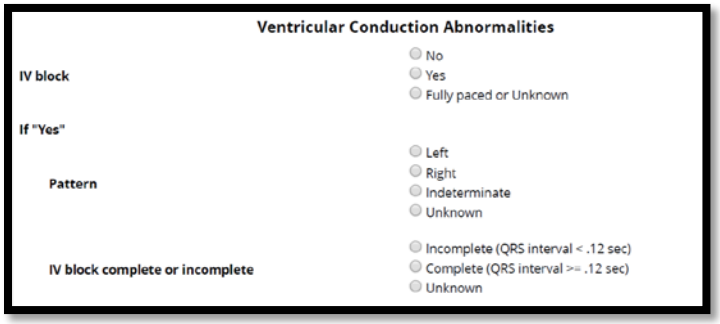
Ventricular Conduction Abnormalities

IV Block

- No *An RSR' pattern in the absence of QRS prolongation should be coded as normal.
- Yes (right or left bundle branch block, details below)
- Fully paced or Unknown

Pattern
- Left [if complete, code MI unknown]
- Right [can code MI]
- Indeterminate (QRS is prolonged, but the pattern is not that of right or left BBB)
- Unknown

IV block Complete or Incomplete
- Incomplete (QRS duration ≥0.10 but <0.12 sec) or (RSR' pattern with QRS ≥ 0.09 sec) [can code MI regardless of pattern]
- Complete (QRS duration ≥.12 seconds
- Unknown



Hemiblock

- No
- Left anterior
- Left posterior
- Fully paced or unknown

Left anterior
- L axis deviation – 60° or less.
- qR complexes in leads I, aVL
- rS complexes in leads II, III, aVF
- Prolonged R wave peak time in aVL > 45ms

Left posterior
- R axis deviation: QRS axis > +120°
- rS complexes in leads I and aVL
- qR complexes in leads II, III and aVF
- Prolonged R wave (slurred) peak time in aVF
- Exclude RVH

WPW syndrome

- No
- Yes (PR ≤.12 sec and slurred upstroke of the QRS (delta wave)
- Maybe (PR ≤.12 and delta wave is possibly present, or delta wave is present but PR marginally short .13 to .14 seconds)
- Fully paced or unknown (i.e., atrial fib)

Arrhythmias

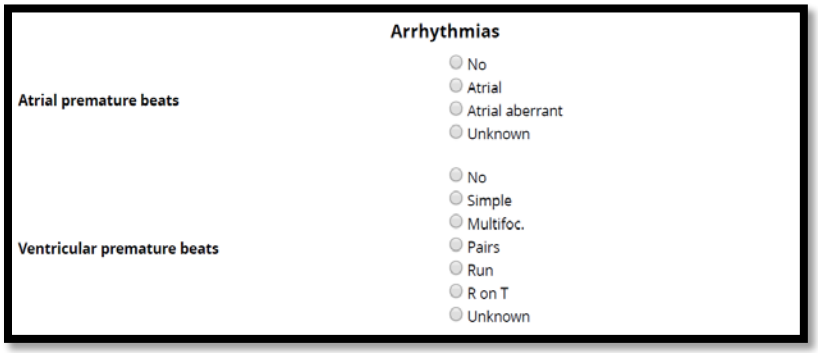
The presence of rhythm disturbances should be made based on examination of the ½ speed rhythm strip which accompanies each ECG.

Atrial premature beats

- No
- Atrial
- Atrial aberrant
- Unknown (i.e., atrial fib)

Ventricular premature beats

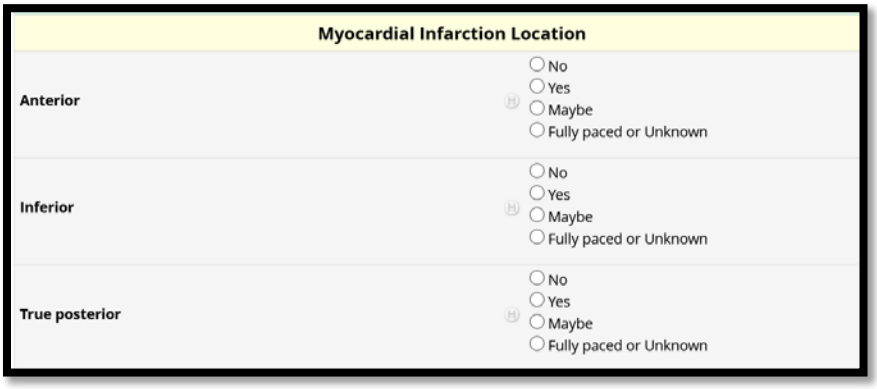
- No
- Simple
- Multifocal
- Pairs
- Run
- R on T
- Unknown



Myocardial Infarction Location

This is determined based on wide (.04 seconds) or deep (1/4 the height of the R wave) Q waves. **All tracings should be compared to the prior exam ECG, which is always provided**.

- New, but small Q waves should also be regarded as suggestive of MI.
- In the right context (e.g., with new Q waves in other leads), loss of R waves in the anterior precordial leads (V3-V6) may be indicative of MI.
- The presence of old Q waves should be coded as Infarction and described in the narrative section as consistent with prior ECG.
- A posterior MI is present when R > S in V1, R is .04 seconds in duration, and an upright T wave is recorded in that lead. When criteria are largely, but incompletely fulfilled, code this item as maybe.
- If complete LBBB or fully ventricular paced, code UNKNOWN for Infarction.



Hypertrophy, Enlargement and Other ECG Diagnoses

Nonspecific S-T segment abnormality

- No
- S-T depression
- S-T flattening
- Other
- Fully paced or unknown

Nonspecific T-wave abnormality (in more than one lead)

- No
- T inversion
- T flattening
- Other
- Fully paced or unknown

Atrial enlargement

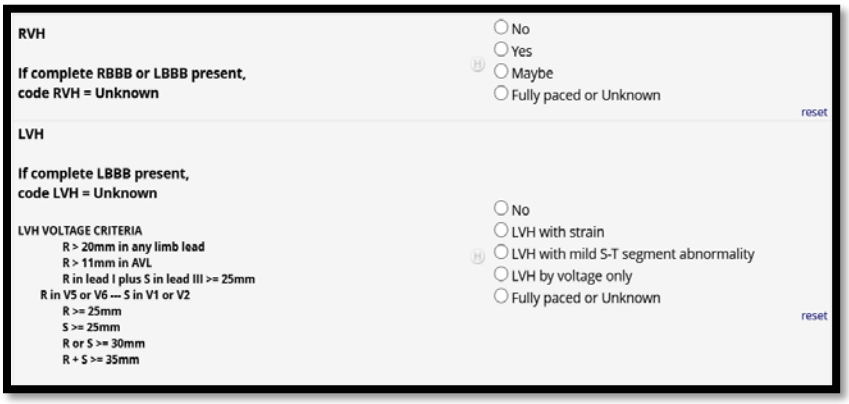
- None
- Left abnormality (terminal portion of the p wave in lead V1 is inverted and measures at least 1mm by 1mm (at normal standardization) [Morris P wave]
- Right abnormality (P wave in inferior leads is peaked with a height of 2.5 mm)
- Both
- Atrial fibrillation or unknown

RVH

- No
- Yes (increased R wave voltage in V1 and increased S wave voltage in V5 in the absence of RBBB. The sum of R in V1 + S in V5 should be at least 10.5mm.)
- Maybe
- Fully paced or unknown (complete RBBB)

LVH

- No
- LVH with strain (increased voltage is present together with strain pattern (down sloping ST))
- LVH with mild S-T segment abnormality (voltage criteria are fulfilled but only mild ST-T flattening)
- LVH by voltage only (no ST abnormality)
- Fully paced or unknown (complete BBB)



Referral Guide for new ECG findings

Call participant's MD **Fax ECG** **Expedite chart**	**Referral (letter)**
•A fib or flutter •high-grade heart block •symptomatic with new ECG findings •ST/T wave depression/elevation	•LBBB •definite new Q waves
•Call participant's cardiologist, or PCP if no cardiologist, to notify of new ECG findings. •Document all participant and provider conversations in REDCap Referral Tracking (M20) or Medical Portion Date (M22). •Follow up by phone with ppt the next workday following all adverse events. Notify Maureen Valentino by email when follow-up call has been made. Document any pertinent info from this call in REDCap if needed. •Document all phone calls **to** participant in PTS Contact Log. •If any barriers to accessing care (e.g. cognitive, language), NP may facilitate appointment.	

Updated November 2021

THE FRAMINGHAM STUDY

CRITERIA FOR EVENTS

1. Cardiovascular Disease

Cardiovascular disease is considered to have developed if there was a definite manifestation of coronary heart disease, intermittent claudication, congestive heart failure, or stroke or transient ischemic attack in the absence of a previous manifestation of any of these diseases. Criteria for all these events are given below. A person having more than one cardiovascular manifestation within the follow-up period is counted as an incident case only at the time of the first event.

2. Coronary Heart Disease

Subjects are diagnosed as having developed coronary heart disease (CHD) if upon review of the case a panel of three investigators (the Framingham Endpoint Review Committee) agrees on one of the following definite manifestations of CHD: myocardial infarction, coronary insufficiency, angina pectoris, sudden death from CHD, non-sudden death from CHD. Persons with pre-existing CHD at Exam 1 are excluded from the population at risk of developing CHD but may be eligible for studies of prevalent CHD. Pre-existing CHD at Exam 1 is identified by any one of the following diagnoses at Exam 1: definite angina pectoris, definite history of myocardial infarction, definite myocardial infarction by electrocardiogram, doubtful myocardial infarction by electrocardiogram, definite coronary insufficiency by electrocardiogram and history.

The various manifestations of CHD are these:

Angina Pectoris

Brief recurrent chest discomfort of up to 15 minutes duration, precipitated by exertion or emotion and relieved by rest or by nitroglycerine is regarded as angina pectoris (AP) if two physicians interviewing the subject at a Framingham clinic visit or the Framingham Endpoint Review Committee, upon review of medical records, agree that this condition was definitely present. This diagnosis is based solely on evaluation of subjective manifestations. Abnormality of the resting or exercise electrocardiogram is not required for this diagnosis.

Myocardial Infarction

Recent or acute myocardial infarction (MI) is designated when there were at least two of three findings:

1) symptoms indicative of ischemia;
2) changes in biomarkers of myocardial necrosis;

3) serial changes in the electrocardiograms indicating the evolution of an infarction, including the loss of initial QRS potentials (that is, development of "pathologic" Q-waves of 0.04 second duration or greater).

An old or remote myocardial infarction is considered to be present when the electrocardiogram shows a stable pattern including a pathologic Q-wave of 0.04 second or greater or loss of initial QRS potential R-wave in those leads in which this would not be expected to occur. Also, an interim unrecognized MI is indicated when changes from a previous tracing show development of loss of R-wave potential or appearance of pathologic Q-waves not otherwise explained, in persons in whom neither the patient nor his physician considered the possibility of MI. If the patient was asymptomatic for chest pain or upper abdominal pain during the interval at which the unrecognized MI occurred, the event is classified as silent, unrecognized. More weight is given to this finding if a T-wave abnormality is also associated with Q-wave abnormality.

An autopsy report showing an acute, new, or recent infarction of the myocardium is accepted as evidence of an incident myocardial infarction. Because it is not possible to date an old infarction found on autopsy, such evidence is not used in the clinical diagnosis of a new event, unless there was an interim clinical event suspected of being an infarction.

Coronary Insufficiency

The coronary insufficiency syndrome is designated when a history of prolonged ischemic chest pain (> 15 minutes duration) was accompanied by transient ischemic S-T segment and T-wave abnormality in the electrocardiographic tracing but not accompanied by development of Q-wave abnormality or by serum enzyme changes characteristic of myocardial necrosis.

Coronary Heart Disease Death

Death from coronary heart disease is diagnosed as either sudden or nonsudden. For a detailed description of these diagnoses, see 6 below.

3. Stroke

The diagnosis of cerebrovascular disease is based on the occurrence of a clinically evident stroke documented by clinical records reviewed by at least two neurologists. Stroke is defined as the sudden or rapid onset of a focal neurologic deficit persisting for greater than 24 hours. Stroke is further categorized into infarction or hemorrhage.

Hemorrhagic Stroke

The diagnosis of subarachnoid hemorrhage is based on a history suggestive of this process such as abrupt onset headache, with or without change in the level of consciousness, and signs of meningeal irritation with or without other localizing

neurological deficits. Intracerebral hemorrhage is diagnosed clinically by the occurrence of abrupt focal neurologic deficit, often with altered level of consciousness and symptoms of increased intracranial pressure. Hemorrhages are confirmed by imaging.

Ischemic Stroke

A diagnosis of cerebral embolism is made when an established source for embolus including atrial fibrillation, rheumatic heart disease with mitral stenosis, recent myocardial infarction, bacterial endocarditis or other known source is determined. A clinical course consistent with embolic infarction or evidence of other systemic embolism may be present. Symptoms are usually rapid with maximal severity at onset.

Antherothrombotic brain infarction is defined as the sudden onset of a focal neurologic deficit lasting longer than 24 hours, in the absence of:
1) known source of embolism (atrial fibrillation, rheumatic heart disease with mitral stenosis, myocardial infarction within preceding six months, bacterial endocarditis);
2) intracranial hemorrhage (intracerebral or subarachnoid);
3) known hypercoagulable states;
4) other disease processes causing focal neurologic deficits (brain tumor, subdural hematoma, hypoglycemia).
Confirmatory imaging supports the diagnosis.

Silent stroke may be documented at the stroke review sessions when a stroke event is determined and an incidental infarct is seen on brain imaging in the absence of a reported clinical event.

Transient ischemic attack

A transient ischemic attack is defined as a focal neurologic deficit of sudden or rapid onset that fully resolves in less than 24 hours.

Stroke Death

Death attributed to stroke is designated when a documented focal neurologic deficit of greater than 24 hours duration preceded death and was responsible for the fatality.

4. Intermittent claudication

Minimum criteria for the subjective diagnosis of intermittent claudication consists of a cramping discomfort in the calf clearly provoked by walking some distance with the pain appearing sooner when walking quickly or uphill and being relieved within a few minutes by rest. This diagnosis is designated if two physicians at a

Framingham clinic visit or the Framingham Endpoint Review Committee, upon review of medical records, agree that this condition is definitely present. A diagnosis of intermittent claudication is based solely on evaluation of subjective manifestations.

5. Congestive heart failure

A definite diagnosis of congestive heart failure requires that a minimum of two major or one major and two minor criteria be present concurrently. The presence of other conditions capable of producing the symptoms and signs are considered in evaluating the findings.

Major Criteria:

1) Paroxysmal nocturnal dyspnea or orthopnea;
2) Distended neck veins (in other than the supine position);
3) Rales;
4) Increasing heart size by x-ray;
5) Acute pulmonary edema on chest x-ray;
6) Ventricular S(3) gallop;
7) Increased venous pressure > 16 cm H_20;
8) Hepatojugular reflux;
9) Pulmonary edema, visceral congestion, cardiomegaly shown on autopsy;
10) Weight loss on CHF Rx: 10 lbs./5days.

Minor criteria:

1) Bilateral ankle edema;
2) Night cough;
3) Dyspnea on ordinary exertion;
4) Hepatomegaly;
5) Pleural effusion by x-ray;
6) Decrease in vital capacity by one-third from maximum record;
7) Tachycardia (120 beats per minute or more);
8) Pulmonary vascular engorgement on chest x-ray.

6. Coronary heart disease death

Death from coronary heart disease is diagnosed as either sudden or nonsudden.

Nonsudden death from CHD

If the terminal episode lasted longer than one hour, if the available information implies that the cause of death was probably CHD, and if no other cause can be ascribed, this is called nonsudden death from CHD. In making this diagnosis, the

review panel uses prior clinical information as well as information concerning the final illness.

Sudden death from coronary heart disease

If a subject, apparently well, was observed to have died within a few minutes (operationally documented as under one hour) from onset of symptoms and if the cause of death cannot reasonably be attributed on the basis of the full clinical information and the information concerning death to some potentially lethal disease other than coronary heart disease, this is called sudden death and is attributed to coronary heart disease.

7. Cardiovascular disease death

This cause of death is designated when any disease of the heart or blood vessels is considered responsible.

8. All-cause mortality

The fact of death is supported by a death certificate. Additional information is obtained from records supplied by hospital, attending physician, pathologist, medical examiner, or family. The Framingham Endpoint Review Committee reviews all evidence to arrive at the cause of death.

Referral Tracking

Is Further Medical Evaluation needed?

- This page is completed by examining NP/MD.
- If referral / further evaluation is indicated, click Yes and the form will appear.
- **Result (Reason for Referral)**

  Click Yes under the applicable referral reason and add specifics if required.

Notification of Referrals

- Participants in the Research Center are typically notified of the referral face-to-face and in the result letter.
- Notify the participant's health care provider by phone of important ECG, BP, or medical findings.
- Once the HCP is notified, the ECG should be faxed and the chart may need to be Expedited. L
- ess urgent findings can be communicated in the result letter only.
- See Referral Guidelines table (end of this section) for specifics.

Referral Guidelines

<table>
<tr><th></th><th>Call participant's MD
(fax ECG if applicable)</th><th>Expedite
(letter)</th><th>Referral</th></tr>
<tr><td>ECG
Report NEW findings</td><td colspan="2">•A fib or flutter
•high-grade heart block
•symptomatic with new ECG findings
•ST/T wave depression/elevation/ T wave inversions (if clinical sxs: Call)
**FAX ECG and expedite chart</td><td>•LBBB
•definite new Q waves</td></tr>
<tr><td rowspan="2">BP</td><td>SBP ≥ 200mmHg or DBP ≥ 110</td><td>SBP ≥ 180 or DBP ≥ 100</td><td>•SBP ≥ 130 or DBP ≥ 80 if not known to have hypertension
•SBP ≥ 140 or DBP ≥ 90 if known to have hypertension and under treatment</td></tr>
<tr><td>•SBP ≤80 mmHg
•SBP ≤ 90 with symptoms of lightheadedness, weakness, fatigue</td><td>•SBP 80-90 without symptoms</td><td></td></tr>
<tr><td colspan="3">Symptomatic (notify RC manager)
<u>Stable</u>:
1) Text Dr. Murabito
2) Activate EMS
3) Call ppt MD
<u>Unstable</u>:
1) Activate EMS
2) Text Dr. Murabito
3) Call ppt MD</td><td>NP identified medical problem (depending on urgency)</td></tr>
<tr><td colspan="4">•Call participant's cardiologist, or PCP if no cardiologist, to notify of findings.
•Document all participant and provider conversations/calls in REDCap Referral Tracking (M20) (or Medical Portion Date (M22)).
•Follow up by phone with ppt the next workday following all adverse events. Notify Maureen Valentino by email when follow-up call has been made. Document any pertinent info from this call in REDCap if needed.
•Document all phone calls to participant in PTS Contact Log.
•If any barriers to accessing care (e.g. cognitive, language), NP may facilitate appointment.</td></tr>
</table>

Updated November 2021

SECOND OPINION GUIDELINES

1. A second opinion is needed when there had been a NEW EVENT since the last FHS examination.

This includes any of the following:

AP / CI / MI / CHF / TIA / CVA / IC

A second opinion is also need in the case of:

AP prior to MI / AP following MI

TIA before or after Stroke

2. For chest pain with any suspicion of AP – 2nd opinion needed
   For chest pain when there is no suspicion of AP – 2nd opinion is not needed

3. For persistent AP or IC — Check if summary of findings reflects confirmed diagnosis of AP,
   If it has been adjudicated as definite AP, 2nd opinion is not needed.
   Otherwise, 2nd opinion is needed.

4. Recurrent event after even-free period – 2nd opinion not needed

(For Participant)

Research Exam Date:
Letter Date: 02/13/2018

,

Dear :

Thank you again for participating in the research examination at the Framingham Heart Study. In your consent form, you gave permission to provide findings of non-genetic research tests to you and/or your physician or other health care provider. We are now providing you and your health care provider some findings as described below.

Please keep in mind that the research examination you had at the Heart Study is not clinical care and the testing is done for research purposes only and should not be relied on to make any diagnosis, treatment, or health planning decisions. The research examination does not take the place of medical care by your own physician or health care provider and cannot be relied upon to identify heart or other health conditions.

Enclosed are some findings from the research examination about your cholesterol/blood glucose measurements and your ECG. These findings have been forwarded to your doctor or health care provider:

If you have any questions, please contact Maureen Valentino, the FHS participant coordinator at the Framingham Heart Study: 508-935-3417 / 800-536-4143.

We look forward to seeing you again and appreciate your support. Your participation in the Framingham Heart Study makes possible our efforts to identify the cause of heart disease and other major health conditions.

Thank you for your continuing support.

Sincerely,

Daniel Levy, MD
Director, Framingham Heart Study

Examiner:

OMB #0925-0216 expiration 7/31/2019

(For Participant's Chart with FHS ID)

Research Exam Date:
Letter Date: 02/13/2018

FHS ID:

,

Dear :

Thank you again for participating in the research examination at the Framingham Heart Study. In your consent form, you gave permission to provide findings of non-genetic research tests to you and/or your physician or other health care provider. We are now providing you and your health care provider some findings as described below.

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Thank you for your continuing support.

Sincerely,

Daniel Levy, MD
Director, Framingham Heart Study

Examiner:

OMB #0925-0216 expiration 7/31/2019

(For Participant MD)

RESEARCH EXAMINATION REPORT
GEN2 Exam 10/Omni Group 2 Exam 5

Name:
DOB:
,
Research Exam Date:
Letter Date: 2/13/2018

Dear :

Your patient named above participated in a research examination at the Framingham Heart Study.

Please keep in mind that the research examination at the Heart Study is not clinical care. The testing is done for research purposes only and should not be relied on to make any diagnosis, treatment, or health planning decisions. The research examination does not take place of medical care by a physician or health care provider and cannot be relied upon to identify heart or other health conditions.

Below are the blood pressure readings on your patient from the research examination. Enclosed are cholesterol/blood glucose measurements and an ECG on your patient.

BLOOD PRESSURE	FIRST READING	SECOND READING
Systolic Blood Pressure		
Diastolic Blood Pressure		

If you have any questions, please do not hesitate to contact me.

Daniel Levy, MD
Director, Framingham Heart Study

Examiner:

OMB #0925-0216 expiration 7/31/2019

(For MD, in Participant's Chart with FHS ID)

RESEARCH EXAMINATION REPORT
GEN 2 Exam 10/Omni Group 1 Exam 5

,

Name:
DOB:
Research Exam Date:
Letter Date: 2/13/2018
ID:

Dear :

Your patient named above participated in a research examination at the Framingham Heart Study.

Please keep in mind that the research examination at the Heart Study is not clinical care. The testing is done for research purposes only and should not be relied on to make any diagnosis, treatment, or health planning decisions. The research examination does not take place of medical care by a physician or health care provider and cannot be relied upon to identify heart or other health conditions.

Below are the blood pressure readings on your patient from the research examination. Enclosed are cholesterol/blood glucose measurements and an ECG on your patient.

BLOOD PRESSURE	FIRST READING	SECOND READING
Systolic Blood Pressure		
Diastolic Blood Pressure		

If you have any questions, please do not hesitate to contact me.

Daniel Levy, MD
Director, Framingham Heart Study

Examiner:

OMB #0925-0216 expiration 7/31/2019

Sociodemographics and Subjective Health

This is a self-reported form. The participant will fill this questionnaire out in Research Center. Once the participant is done with the form a staff member will review the form for completeness. If any blanks are left the question will be flagged and the participant will be asked to fill in the blank.

Question 1: What is your current marital status?

1=single/never married,
2=married/living as married/living with partner
3=separated
4=divorced
5=widowed
9=prefer not to answer

Question 2: What is the highest degree or level of school you have completed? (if currently enrolled, mark the highest grade completed, degree received)

0= no schooling
1=grades 1-8
2=grades 9-11
3=completed high school (12^{th} grade) or GED
4=some college but no degree
5=technical school certificate
6=associate degree (Junior college AA, AS)
7=Bachelor's degree (BA, AB, BS)
8=graduate or professional degree (master's, doctorate, MD, etc.)
9=prefer not to answer

Question 3: Please choose which of the following best describes your current employment status?

0=homemaker, not working outside the home
1=employed (or self-employed) full time
2=employed (or self-employed) part time
3=employed, but on leave for health reasons
4=employed, but temporarily away from my job
5=unemployed or laid off
6=retired from my usual occupation and not working
7= retired from my usual occupation but working for pay
8= retired from my usual occupation but volunteering
9=prefer not to answer
10=unemployed due to disability

11= full-time student

Question 4: What is your current occupation? Write in

_____

Question 5: Using the occupation drop down list, choose the code that best describes your occupation.

Question 6: Please select which income group best represents your combined family income for the past 12 months.

1=under $20,000
2 =$20,000 – $34,999
3 =$35,000 – $54,999
4 =$55,000 – $74,999
5 =$75,000 – $100.000
6 =over $100,000
99=prefer not to answer

Question 7: How many people are supported by this income?

Question 8: Do you have some form of health insurance? 0=No, 1=Yes
If the participant answers yes, make sure that the participant circles what type of insurance they have from the insurance plan list.

Question 9: Do you have prescription drug coverage

OCCUPATION CODING

01= Homemaker
02= Retired
03= Self Employed Business Owner
04= M.D. / Dentist
05=Lawyer/ Judge
06= Psychologist / Social Worker / Mental Health Counselor
07= Scientist / Research
08= Engineer / Computer Science
09= Banker / Accountant
10= Manager / Consultant (e.g. Production Manager)
11= Administer (e.g. Personnel)
12= Educator
13= Nurse / Medical Personnel
14= Laboratory Technician
15= Physical / Occupational / Speech Therapist
16= Secretary/ Clerk / Data Entry
17= Retail / Cashier
18= Sales / Marketing / Insurance
19= Realtor
20= Writer / Editor
21= Artist / Graphic Designer / Craftsperson
22= Musician
23= Police / Fire / Security / Military
24= Factory / Assembly
25= Mechanic
26= Restaurant / Food Worker
27= Skilled Labor (e.g. Plumber, Carpenter, Painter, Hairdresser)
28= General Labor (e.g. Custodian, Delivery, Mailman, Truck Driver)
29= Heavy Labor (e.g. Construction, Landscaping)
30= Clergy (minister, Priest, Rabbi)
31= Sports Pro / Coach / Exercise Instructor
32= Statistician
33= Student
88= Other

SF-12®
Self-Administered

What is the SF-12®?

The SF-12® is a multipurpose short-form (SF) generic measure of health status. It was developed to be a much shorter, yet valid, alternative to the SF-36® for use in large surveys of general and specific populations as well as large longitudinal studies of health outcomes. All SF-12® items came from the SF-36®.

The SF-12® has become one of the most widely used instruments for purposes of monitoring the health of both general and specific populations because it is substantially shorter than SF-36®. It has been adopted for many large population outcomes monitoring efforts that did not include the SF-36® because of its length. More than 1 million SF-12® surveys were administered within a year of its release and the SF-12® has been selected for inclusion in the National Committee for Quality Assurance (NCQA) *Annual Member Health Care Survey* (Version 1.0), which NCQA and many large employers require for accreditation. These trends confirm the expected practical advantage of the SF-12®.

The SF-12® includes one or two items from each of the eight health concepts Thus, the SF-12® measures eight concepts commonly represented in widely used surveys: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health (psychological distress and psychological well being). Both standard (4-week) and acute (1-week) recall versions are available.

Source: Ware, J., Kosinski, M., Keller, S.
"SF-12®: How to Score the SF-12® Physical and Mental Health Summary Scales" (Third Edition: September 1998)
Quality Metric Incorporated, Lincoln, Rhode Island and The Health Assessment Lab, Boston Massachusetts

Reference: Ware, J., Kosinski, M., Keller, S.
"A 12-Item Short-Form Health Survey – Construction of Scales and Preliminary Tests of Reliability and Validity"
Medical Care, Volume 34, Number 3, PP 220-233 ©1996 Lippincott-Raven Publishers

Note: This form is tech administered on offsite visits. These questions cannot be answered by a proxy.

SF-12 Health Survey

The Quality of Life form has twelve questions and is designed to collect information about the participant's perceived physical and emotional health, as they relate to quality of daily living.

Q1 asks the participant to rank his/her general health on a five-point response scale: *Excellent, Very Good, Good, Fair, Poor*.

Q2 and Q3 address the extent to which a participant's health limits his/her activities regarding moderate activities and climbing stairs, using a three-point response scale: *No- not limited, Yes- limited a little, Yes- limited a lot.*

Q4-Q7 ask the participant to assess whether physical and emotional problems have impacted his/her ability to perform work tasks or regular daily activities during the previous four weeks. A *Yes* or *No* response is required.

Q8 asks the participant how much pain interfered with his/her normal work during the previous four weeks, using a five-point response scale: *Not at all, A little bit, Moderately, Quite a bit, Extremely*.

Q9-Q12 ask the participant how he/she has felt during the previous four weeks, using a six point response scale: *All of the time, Most of the time, A good bit of the time, Some of the time, A little of the time, None of the time*.

PLEASE READ

INSTRUCTIONS FOR COMPLETING THE FOOD FREQUENCY QUESTIONNAIRE

An important part of the Framingham Heart Study is the completion of this Food Frequency Questionnaire. It is designed to measure your dietary pattern over the past year.

Thank you so much for participating in this research study.

Please complete this form and bring it with you at the time of your appointment.

1. **Please use a #2 pencil.**
2. Do not leave any questions blank. Every line must have a circle colored in, except as noted below. If an item or section does not apply to you, please color in a circle that is labeled, "No" or "Never." The exceptions, which can remain blank, include section #2 (if you do not take other supplements) and section #14 (if you do not eat foods not listed elsewhere on the form at least once per week).
3. Please fill-in only one circle per item, except for section #5 (form of margarine or spread), last item of section #6 (Type of salad dressing) and sections #9 and #10 (What kind of fat is usually used). These questions ask about the form or types of fats ***typically*** used so one response is ideal, but if more than one type of fat is frequently used, then multiple responses are allowed.
4. Make sure that all erasures are complete.

Thank you for taking the time to fill out this form.

Guidelines for Review of Willett Food Frequency Questionnaire

The purpose of the Willet Food Frequency Questionnaire is to obtain information about what the participant usually eats and drinks. The questions review specific foods and portion sizes, to find out how often, on average, the specified amount was eaten or drunk during the past year. The Willet Food Frequency Form is completed prior to the participant's clinic visit.

Special arrangements may be made if the participant is illiterate, has problems reading, cannot read English, or is unable to answer the questions accurately due to physical or cognitive disabilities. This may be evident for example, the answer sheet has all circles filled out in the first column or is not filled out at all.

1. Check that there are no staples, rips, tears, or writing other than where indicated. If so, the form must be redone.

2. Make sure that the form is completed with a #2 pencil.

3. Check that circles are filled in completely - no Xs, checkmarks, etc.

4. Check that a response has been filled in for every line. If never used, fill in that circle.

5. Check that there is only one response for every line.

6. For vitamins, make sure the brand, the dose and how long taken is written in the spaces provided.

7. Make sure that all extra foods are written in the numbered spaces (up to 4 items) with complete information.

8. Make sure that what is written in the extra foods section is not something that is already in another part of the questionnaire.

9. Make sure to check for completeness of I.D. number.

10. Make sure to stamp the date on top when the participant brings in the form.

Instrucciones para rellenar la forma sobre la dieta "Food Frequency Questionnaire"

Muchas gracias por participar en este estudio. Una parte importante del mismo es el cuestionario sobre su dieta (Food Frequency Questionnaire) que ha sido diseñado para medir su patrón de alimentación durante el último año.
Por favor llene esta forma y tráigala con usted el día de su cita.

Desafortunadamente solo tenemos esta forma en Inglés. Si cuenta con alguien que le pueda ayudar a llenarla se lo agradeceríamos mucho, si no, por favor traiga esta forma a la clínica y con gusto aquí le ayudaremos a completarla. Es muy importante que sea contestada con la mayor exactitud posible!

Por favor:
1.- Use LAPIZ para rellenar los círculos en su totalidad, indicando su respuesta.

2.- No deje ninguna respuesta sin marcar. Si la pregunta o sección de preguntas no aplican a usted, rellene los círculos "never" (nunca).

3.- No separe, engrape ni destruya esta forma.

4.- Si necesita cambiar una respuesta, por favor borre completamente el círculo con la respuesta equivocada.

GRACIAS!

Sleep Questionnaire

Self-Administered in Research Center/Tech-Administered Offsite

1. In Research Center exams, the staff must check the form for completeness.
2. If the participant is cognitively impaired the questions will not be asked of the participant or of their proxy due to the length of the examination.

Mini-Mental State Exam (MMSE)

Tech-Administered

Background and Rationale:

Cognitive function may decline as a result of certain risk factors (e.g. hypertension, elevated cholesterol, cardiac arrhythmias). This in turn could adversely impact the physical functioning and quality of life of older adults. Dementia is a major illness and cause of disability among the elderly. Risk factors that have been identified for cardiovascular disease (e.g., smoking, diabetes, hypertension, high cholesterol, atherosclerosis, etc.) are also risk factors for some types of dementia, such as Vascular dementia and Alzheimer's dementia. The Mini-Mental State Exam (MMSE) is a widely used test of cognitive function among the elderly; it includes tests of orientation, attention, memory, language and visual-spatial skills.

The MMSE is a 30 point test that was designed as a short screening measure of cognitive status. The goal of the test was to determine if people show signs of cognitive impairment. It has come to be used widely as a screening test for progressive dementing disorders, such as Alzheimer's disease.

Within Framingham, it is used to determine if someone is showing changes in cognitive function, and we do so by looking for a drop in the MMSE score compared to previous exams. If there is a drop of 3 points or more from the immediately preceding exam, we would invite the participant into the Dementia study for further neuropsychological testing and a neurological exam. If there is a drop of 5 points or more across all exams, this will also trigger a request for further follow up by the Neuro group.

While the MMSE has been useful in serving as a screening tool, it also has some significant limitations. One major issue is that younger and/or highly educated people are likely to score the maximum score of 30. This is known as a ceiling effect - even when people might be starting to experience real changes in cognition, the MMSE might not pick it up until much later on. The other major limitation with the MMSE is that the test is not diagnostic and a poor score does not always indicate the presence of dementia. Or, even if the score suggests the participant may have dementia, it does not inform the question of what type of dementia. It is very hard to determine with any level of confidence what areas of cognition are impaired based on MMSE performance. Sometimes, researchers do try to look at specific items on the test, and determine cognitive-domain specific deficits. For example, poor performance on the recall item may lead some to decide there is a memory problem.

If there are any concerns regarding the participant's cognition, notify the Research Center physician and refer the participant for further assessment with the Neuro group. The Clinic physician should complete a Referral Form and give to the Neuro Program Manager, xxxxx after the exam. Referral forms can be found in the appendices.

If a participant has been seen by the Neuro group previously, it is indicated on the PTS Bookings screen. Sometimes a family member will tell the recruiters that there is a memory issue.

During the admitting process, if the participant has trouble answering questions (i.e., children's names, sibling's names, etc.) the Admitter will notify the Research Center staff who will then notify the Research Center physician.

****NOTE: Questions cannot be answered by a proxy.****

Methods:

1. The MMSE asks questions to ascertain cognitive status. Responses are scored:
   0 = incorrect
   1 = correct
   9 = test item not administered or invalid

2. If a response is ambiguous, the interviewer records the response in the text field and a decision about how to score the item can be made later. Please refer all questionable responses to the neuropsychologists (currently Sherral Devine or Rhoda Au)

3. When a participant is incapacitated by blindness, has a functional disability, is illiterate, or is otherwise unable to respond to a question, the interviewer should code "9" and specify the problem and questions involved. (See box at end of this document titled "**Factors Potentially Affecting Individual Test Items.")**

Expanded Scoring Instructions for Mini-Mental Exam:

Important note: Sometimes a participant might produce a response that is not a word (i.e. a neologism) but has been responding with intelligible responses on previous items (right or wrong). In this case the items should be scored **0**. The key to differentiating a **0** or a **9** is consistency within test. If a person has a speech abnormality, such as aphasia or dysarthria, across all items, most (or many) responses will be unintelligible (code = 9). If a person is, for example, demented, he/she may produce a flow of intelligible responses with occasional unintelligible responses (code = 0). A "**9**" must represent situations in which (1) the EXAMINER is not sure whether the participant responded correctly (because of slurred speech, severe stuttering, etc.), or (2) the participant has some other factor that prevents test item administration (such as an inability to administer the *copy this figure* test item to a right-handed person who has right-handed paralysis, or to someone who has a visual impairment or inability to hear). A **"9"** is also used when the test question was administered, but for some reason it is invalid. See "Factors Potentially Affecting Mental Status Testing" at the end of this document.

Scoring for Administered Individual Items:

Score **0** for the following reasons: (applies only if a test item is administered)

- Incorrect response

- I don't know
- Unintelligible response in context of other intelligible responses

Score **9** for the following reason:

- When test item was not administered (refused or inability because of physical limitations),
- When the test is invalid (e.g., experimenter error, environmental distraction), or
- When the subject's response is uninterpretable (response could be correct, but tester is unable to discern the response).

Questions: Scripts and Procedures for Each Question:

Introduce the digital pen: Prior to starting the MMSE, provide the participant with the following instruction: ***This is a special kind of pen. It writes just like any other pen, but we have found, especially if it goes horizontal to the table [demonstrate this], it might vibrate and buzz. This is harmless. If it does happen, please try to hold your pen a little more vertically [demonstrate this] and continue with what you were doing.***

Introductory Script**:** ***I'm going to start by asking questions that require concentration and memory. Some questions are more difficult than others and some will be asked more than one time.***

Read each question on the screen.
Record the response on the screen.

NOTE: The range of possible points is written after each question.

1. What is the date today? (sum of correct answers for month (1 pt), day (1 pt) and year (1 pt))

If any parts (month, day, year) are missing, ask for them specifically (e.g. ***Can you also tell me what year it is?***)

If participant supplies part or all of the date (e.g. month and day, or month, day, and year), record as appropriate. Do not prompt for specific parts if the participant has already provided a response.

2. What is the season? **(1 = correct)**

Since distinctions between seasons can be difficult during certain months, one week leeway is allowed on either side of the actual date.

MMSE ACCEPTABLE ANSWERS FOR "WHAT IS THE SEASON"?

2019

Month	Correct Response	Acceptable Dates (2 Seasons)
April	Spring	n/a
May	Spring	n/a
June	Spring or Summer	6/14/19 – 6/28/19
July	Summer	n/a
August	Summer	n/a
September	Summer or Fall/Autumn	9/16/19 – 9/30/19
October	Fall/Autumn	n/a
November	Fall/Autumn	n/a
December	Fall/Autumn or Winter	12/14/19 – 12/28/19

2020

Month	Correct Response	Acceptable Dates (2 Seasons)
January	Winter	n/a
February	Winter	n/a
March	Winter or Spring	3/12/20 – 3/26/20
April	Spring	n/a
May	Spring	n/a
June	Spring or Summer	6/13/20 – 6/27/20
July	Summer	n/a
August	Summer	n/a
September	Summer or Fall/Autumn	9/15/20 – 9/29/20
October	Fall/Autumn	n/a
November	Fall/Autumn	n/a
December	Fall/Autumn or Winter	12/14/20 – 12/28/20

3. What day of the week is it? (1 = correct)

4. What town, county, and state are we in?

(sum of correct answers for town (1 pt), county (1 pt) and state (1 pt))

If the participant is from out of town or out of state, it is acceptable for them to respond with the county they live in. It is okay to prompt them if they live out of the area.

For offsite visits, refer to the section of the manual titled "New England Counties" for a complete list of all counties.

5. What is the name of this place? (1 = correct)

Any appropriate answer is okay. (Possible acceptable responses = FHS, Perini, Mt. Wayte).

On home visits, the examiner can ask, *What is the address of this place? (Possible acceptable responses = Nursing Home, my house, or their address).*

6. What floor of the building are we on? (1 = correct)

Research Center Visit = 1st Floor. If they say "Main Floor," repeat the question adding "now."

7. I am going to name 3 objects. After I have said them I want you to repeat them back to me. Are you ready? *Apple, Table, Penny.* ***Could you repeat the three items for me?***

(sum of correct responses: Apple (1 pt), Table (1 pt) and Penny (1 pt))

Record and score (total number of correct words) the participant's response to the first presentation of the words (i.e., if multiple presentations are given, score only the first).

If, after scoring the first attempt, the participant has not learned the 3 objects, repeat the list of objects up to 6 times until he/she has learned them.

After the participant responds correctly with all three words, say:

Remember what they are because I will ask you to name them again in a few minutes.

Make sure participant is attentive when beginning the question.

Read the list of objects slowly. DO NOT REPEAT ITEMS UNTIL AFTER THE FIRST TRIAL.

If participant asks you to repeat the 3 items, respond, *Can you tell me the items I just mentioned?* or *Just do the best you can*.

The participant can repeat the words in any order. As long as they say the word, they get the point for that word. Maximum score is 3 points.

Occasionally hearing impairments prevent subjects from correctly hearing test questions (for example, when asked to repeat three items, *apple, table, penny,* they may repeat *April, tablet, pencil* -- these alternate responses should be accepted both under the repetition and recall conditions).

8. Now I am going to spell a word forward and I want you to spell it backwards. The word is WORLD. W-O-R-L-D. Please spell it in reverse order. Write in all the letters the participant says, in the order they were said _____.

(letters are entered and computer scored later)

Read the question slowly. Where *world* has hyphens between the letters, spell out the word.

Repeat the spelling if necessary.

If the participant spells the word forward rather than in reverse, they can be cued *once with a reminder to spell it backwards ("Remember to spell it backward").*

9. What are the 3 objects I asked you to remember a few moments ago?

(sum of correct responses: Apple (1 pt), Table (1 pt) and Penny (1 pt))

Items may be repeated in any order.

10. What is this called? (Watch). (1 = correct)

Show the wristwatch to the participant

Correct responses include: watch, wristwatch, timepiece

11. What is this called? (Pencil). (1 = correct)

Show the pencil to the participant. NOTE: the pencil should be a standard sharpened wooden pencil with eraser.

Correct responses include: Pencil, number 2 pencil

12. Please repeat the following: No ifs, ands or buts. (1 = correct)

Enunciate clearly -- include the "**S**" at the end of *if<u>s</u>, and<u>s</u>, or but<u>s</u>,* (if you think the participant heard you but repeated it incorrectly, make a note of what was missed and score **0**).

Allow only **one** attempt.

Score as incorrect if the participant did not repeat the phrase <u>exactly</u>.

Occasionally hearing impairments prevent participants from correctly hearing test questions. In the case of repeating *no ifs, ands, or buts,* some judgment must be made on the part of the examiner as to whether the participant could hear the "***s***" or not.

13. Please read the following and do what it says. (1 = correct)

Hand participant the "Please Close Your Eyes" card.

The participant may read the sentence out loud or silently. It is not necessary for the sentence to be read out loud if the participant performs the function properly.

Score as correct if the participant closes his/her eyes.

14. Please write a sentence. (1 = correct)

See procedures for using the digital pen below

The instruction can be repeated if necessary.

Score as correct if the participant wrote a complete sentence as directed.

Score as correct if the participant is cognitively able to dictate a sentence but is physically unable to write it. In this case the examiner should write the dictated sentence and make a note that it was dictated.

Written commands, such as *sit down*, where the subject is implied, are considered correct responses.

Spelling and/or punctuation errors are not counted as errors.

15. Please copy this drawing. (1 = correct)

If the participant asks if the figures should be drawn separately or together the examiner should respond, *Draw the figures as you see them.*

To be correct, each pentagon must have 5 sides and there must be an overlap that forms a four-sided figure.

16. Take this piece of paper in your right hand, fold it in half with both hands, and put it in your lap.

(sum of correct actions: right hand (1 pt), fold with both hands (1 pt) and put in lap (1 pt))

(If participant is unable to use right hand because of physical disability, you can alter instructions to read "Take this piece of paper in your left hand, fold it in half with your left hand, and put it in your lap". The goal is to see whether the subject is able to follow a 3-step command, so this variation to the directions to accommodate subject's physical limitations is allowable.)

Read the full statement **BEFORE** handing the paper to the participant.

DO NOT direct the paper to participant's right side. Hold the paper in front and have the participant reach out to take it. Observe which hand is used.

DO NOT repeat instructions or coach participant. Only repeat if the examiner felt it was not heard or if instructions were not given clearly (just repeat the directions in full as they were the first time).

Give one point for each of the commands that were properly followed (max = 3)

Factors Potentially Affecting Mental Status Testing

The examiner noted the following factors that may have affected MMSE performance

No	Yes	Maybe	Unknown	Factor
0	1	2	9	Poor hearing
0	1	2	9	Poor vision
0	1	2	9	Not fluent in English
0	1	2	9	Illiteracy or low education
0	1	2	9	Psychological factors (e.g., depression, anxiety, frustration)
0	1	2	9	Poor effort
0	1	2	9	Difficulty understanding instructions
0	1	2	9	Other (describe):

****Procedures for using the digital pen****

On the top of the page, in the box, write the participant's ID and the date. It is absolutely essential that this identifying information is ONLY written within the box.

Fold the paper in half. Present the top half to the participant and ask them to write a sentence (see #14 above).

Turn over the paper and present the side with the drawing of the pentagons, and ask participant to copy the figure (see #15 above).

Reasons the test item was not administered or is invalid (i.e., coded as "9"):

Factors Potentially Affecting Individual Test Items

1 = poor hearing
2 = poor vision
3 = Not fluent in English
4 = Illiteracy or low education
5 = physical limitation (describe)
6 = depression
7 = anxiety
8 = fatigue/frustration
9 = refused
10 = poor effort
11 = difficulty understanding instructions
12 = response unintelligible
13 = environmental distraction (describe)
14 = experimenter error
15 = other (describe)

2021

Month	Correct Response	Acceptable Dates (2 Seasons)
January	Winter	n/a
February	Winter	n/a
March	Winter or Spring	3/13/2021 – 3/27/2021
April	Spring	n/a
May	Spring	n/a
June	Spring or Summer	6/13/2021 – 6/27/2021
July	Summer	n/a
August	Summer	n/a
September	Summer or Fall/Autumn	9/15/2021 – 9/29/2021
October	Fall/Autumn	n/a
November	Fall/Autumn	n/a
December	Fall/Autumn or Winter	12/14/2021 – 12/28/2021

Offspring Exam 10: Short Examination/Split Exam

A short exam is completed when a participant requests an abbreviated exam (usually up to 2 hours of testing). A split exam is completed when a participant requests to do an examination in 2 visits.

The priority of exam procedures is listed below:

I. Informed Consent & Tracking Procedures

1) Informed Consent
2) Release of Health Information for Research Purposes
3) Tracking Information Form

II. Clinical Measurements & Procedures

1) Lab
   a. Blood
   b. Urine
2) Anthropometrics
   a. Weight
   b. Height
   c. Waist at Umbilicus
   d. Hip
3) ECG
4) Tech Administered Questions

III. Physician-Administered Medical History and Physical Exam

1) Medical History
2) Resting Blood Pressure
3) Physical Exam

IV. Self Administered Questionnaire

If time permits for a short exam, the participant will undergo Tonometry, Observed Performance, Fibroscan and/or Pain Assessment

If the participant chooses to have a split exam a second date will be arranged to complete all of the remaining testing for the exam cycle.

Call Backs/ Split Exams
Offspring Exam 10

Participants Name / I.D : **Second Appointment Date:**

Exam Date: **Recruiter's Initials:_____**

***Check Box to indicate which test(s) will be completed on the second visit.**

	TEST:	**APPROXIMATE TIME:**
___	MD Questionnaire/ Physical Exam	30 Min.
___	Anthropometry (Ht, Wt, Waist/Hip/Hand Grip)	15 Min.
___	Self-Administered Questionnaires	15 Min.
___	Tech Administered Questions	15 Min.
___	MMSE	10 Min.
___	Urine	5 Min.
___	Lab	15 Min
___	ECG	10 Min.
___	Walk Test	10 Min.
___	Fibroscan	15 Min.
___	Tonometry	40 Min
___	Pain Assessment	20 Min.
___	Brain Health	30 Min.
___	Bone	15 Min.
___	eFHS	20 Min.

- Why did this participant leave early?

- Which Technician did this participant work with most?

Elevated Blood Pressure

If, during a home visit the blood pressure is:

> **200/110** a call is made to a FHS physician who will notify the participant's personal physician. The chart will be marked "expedite" so that the letter to the personal physician is sent out ASAP.

> **180/100** the chart is expedited

-The Referral sheet is completed to note that contact was made to an FHS MD during the exam.

-If a phone contact was made by an FHS MD to the participant's personal physician, the FHS MD is to complete a "Record of Telephone Encounter" form.

If, during a nursing home visit the blood pressure is:

> **140/90** inform the nurse caring for the participant or the charge nurse

> **180/100** inform the nurse caring for the participant or the charge nurse.
> The chart will be marked "expedite" so that the letter to the personal physician is sent out ASAP.

Framingham Heart Study Gen 2 Exam 10 Offsite Visit – Checklist

1. PRE OFFSITE VISIT Checklist

Labels go here

- ❑ Call to confirm appointment (1-2 days before) Remind ppt to wear button down shirt or button down pajama top
- ❑ Tablet Charged; take Charger

- ❑ Upload Participant Information

- ❑ BP Equipment: BP monitor, cuffs, stethoscope

- ❑ Tech Equipment
  - ✓ Tablet: charged and participant information uploaded, charger
  - ✓ Admitting Form
  - ✓ Consent Form (paper copy)
  - ✓ Medical Release Form (paper copy)
  - ✓ ECG machine and supplies (include Heart Square)
  - ✓ Tape Measure
  - ✓ Scale
  - ✓ Hand Grip
  - ✓ MMSE Pen and Paper
  - ✓ Ancillary Studies
  - ✓ Red gift bags
  - ✓ Gloves
  - ✓ Mask
  - ✓ Thermometer

** Paper form of RC kept in NP bag and Tech bag

Framingham Heart Study Gen 2 Exam 10 Offsite Visit – Checklist

2. DURING OFFSITE VISIT Checklist

Labels go here

- ❑ Covid Screening
- ❑ Consent Form, Health Proxy, Medical Release Form

- ❑ NP
  - ✓ Call to do Med Hx or make appt for NP to call

- ❑ Tech
  - ✓ Weight
  - ✓ Hips/Waist Measurement
  - ✓ ECG
  - ✓ Hand Grip/Walk
  - ✓ Questionnaires on RedCap
  - ✓ BP
  - ✓ MMSE
  - ✓ Self-Administered Questionnaire
  - ✓ Give FFQ
  - ✓ Ancillary Studies (if possible)
  - ✓ EXIT INTERVIEW
  - ✓ Give red bag

Framingham Heart Study Gen 2 Exam 10 Offsite Visit – Checklist

3. POST OFFSITE VISIT Checklist

Labels go here

- ❑ Upload Data

- ❑ Shred copies of participant records (if applicable)

- ❑ NP
  - ✓ Review ECG (contact participant's PCP if new changes to ECG)
  - ✓ Complete participant letter in RedCap
  - ✓ Give chart to Barbara

- ❑ Tech
  - ✓ Take pictures of meds (computer in Research Center Float Desk); delete pictures from tablet
  - ✓ Transmit ECG to MUSE
  - ✓ Print ECG and put (2) in Chart
  - ✓ Give chart to NP
  - ✓ Put tablet on charger
  - ✓ Restock bag, if needed
  - ✓ Put Admit form in chart
  - ✓ Clean everything
  - ✓ Give Daily Sheets to:
    - o Maureen? And?
    - o On top of chart
    - o Ancillary Studies: Tonometry, Fibroscan, Pain Assessment, Brain Health

During HV Checklist Local

- ❑ Covid Screening
- ❑ Ppt info
- ❑ Research Proxy
- ❑ Consent
- ❑ Medical release form
- ❑ Admitting form
- ❑ Med pics
- ❑ Weight/anthro
- ❑ EKG
- ❑ Walk test
- ❑ Hand grip
- ❑ BP
    - Time Start:
    - Time End:
    - Cuff:
        - 1st
        - 2nd
- ❑ Tech Questions
- ❑ Pain Questions
- ❑ T20 (eFHS)
- ❑ SAQ
- ❑ Tech portion date
- ❑ Exiting
- ❑ Red bag
- ❑ Bring everything out except blood
- ❑ Blood draw

Notes about visit:

During HV Checklist Overnight

- ❑ Covid Screening
- ❑ Ppt info
- ❑ Research Proxy
- ❑ Consent
- ❑ Medical release form
- ❑ Admitting form
- ❑ Med pics
- ❑ Weight/anthro
- ❑ EKG
- ❑ Walk test
- ❑ Hand grip
- ❑ BP
    - Time Start:
    - Time End:
    - Cuff:
        - 1st
        - 2nd
- ❑ Bring out EKG / hand grip bags
- ❑ Bring in blood draw equipment / centrifuge
- ❑ Draw blood
- ❑ Set up centrifuge
- ❑ Tech Questions
- ❑ Pain Questions
- ❑ T20 (eFHS)
- ❑ SAQ
- ❑ Package up blood draw materials
- ❑ Tech portion date
- ❑ Exiting
- ❑ Red bag

Notes about visit:

Offspring Exam 10 - Offsite Exam Components

Section I: Informed Consent & Tracking Procedures

1) Informed Consent
2) Waiver of Informed Consent
3) HIPPA - Release of Health Information for Research Purposes
4) Admitting Form
5) Research Proxy

Section II: Clinical Measurements & Procedures

1) **Anthropometrics**
    a. Weight
2) **ECG**
    a. ECG
3) **Observed Physical Performance**
    a. Hand Grip Test
    b. Measured Walks

Section III: Tech-Administered Questionnaires

1) **Cognitive Function**
    a. MMSE
2) **Physical Function**
    a. KATZ-ADL Scale
    b. Rosow-Breslau
    c. NAGI
3) **Depressive Symptoms**
    a. CES-D
4) **Physical Activity Questionnaire**
    a. Exercise
5) **Other**
    a. Fractures
    b. Proxy Form

Section IV: Medical History and BP

1) Medical History
2) Resting Blood Pressure

Section V: Self-Administered Questionnaires

1) Socio-demographics
2) SF12 Health Survey
3) Sleep Questionnaire
4) Bleeding Questionnaire

Section VI: Exam Completeness

1) Referral Tracking & Adverse Events
2) Exit Interview

Scheduling a PPT in PTS

1. Schedule appointment with PPT.
2. Put appointment into 1. Roster, 2. Referral, 3. Booking screens.
3. IN ROSTER SCREEN … change date (survival date) to date you spoke with PPT.
4. IN ROSTER SCREEN…put what was done, i.e. booking (this is the 1st line that is looked at).

REFERRAL SCREEN

It has to be noted what it was scheduled at i.e. a 6 code like 61 = home visit.

BOOKING SCREEN

1. Click on new record at the end of booking screen.
2. Put in Full Date 12/20/2013 space then time (military time) 13.30 (1.30pm).
3. Put in # for exam .e.g. 9.
4. Exam type. E.g. Nursing home visit or home visit.
5. Exam stat… is either current or canceled.
6. Exam location e.g. home or nursing home.
7. Confidential comment can be removed if not pertaining to exam. These comments are carried over from previous exams.
8. Rescheduled… put in if it is a rescheduled or not.
9. Alternate address… This area is where you can put comments that are important to person doing the home visit. Such as speech issues, wheel chair. Etc. Be careful these comments will print on the apt schedule, and roll over from previous exams.
10. PUT IN ITNITALS (ST) AND THEN HIT UPDATE. If the initials are not entered it will not save, and you will not be able to print appointment letter.

CRYSTAL REPORTS

This is where the schedule is printed from

1. Go to Recruiting / Admitting
2. Click on book_off report.
3. Put in Date.. click OK
4. Print from printer icon on side.
5. Be sure to **log off** when finished.

Crystal Report to print CALL BACK LIST

1. Click on call back reports.
2. Enter ID type e.g. 1 for Off spring and also Referral Code you are requesting, i.e. 39 or 31.
3. Then hit ok and print.
4. Again **log off** when finished.

To copy and paste info in the screen , highlight ,HIT Ctrl and c move curser to where you need and hit Ctrl and v.

Offsite Scheduling: Cognitive Impairment:

When scheduling an offsite exam, the same procedure should be used as is done when scheduling a research center exam. The recruiter should be checking the consent status, notes on the comment line and the referral screen for any indications of impairment.

If a greater degree of impairment is suspected, then the Research Proxy or LAR should be contacted. The exam should be described in detail to the designated representative and permission to see the participant established. Any concerns about components of the exam that might be of issue should be documented at the recruitment call to insure they are eliminated at the offsite visit. The proxy for the participant should always be asked if they would like to be present for the exam and their schedule accommodated.

If the research proxy or LAR does not wish to be present, the procedure to obtain consent from the proxy should be established prior to scheduling the exam.

If family members refuse the exam, ask if they are willing to do a telephone health history update.

Note: At the time of the appointment if the participant refuses to have the exam his or her objections will be honored.

Cognitive Impairment Identified at the Offsite Visit

In cases where the participant is scheduled for an offsite and at the scheduled visit impairment is determined, a Waiver should be instituted and the components of the exam allowed under Waiver can be administered.

Note: At the time of the appointment if the participant refuses to have the exam his or her objections will be honored.

The recruitment department should be notified of suspected cognitive status for proper documentation in PTS and to determine if a Research Proxy or LAR should be notified.

Preparation for an Off-site Examination

A. Supplies

The following supplies should be brought with you on an offsite visit:

1 Portable EKG machine
1 Portable EKG acquisition module
1-2 Packs of EKG electrodes
1 Heart square
Alcohol wipes
Gauze
Adhesive remover pads
3 Blood pressure cuffs; large adult, adult and pediatric (Latex Free)
1 Pocket Aneroid Sphygmomanometer
1 Littman Classic II Stethoscope
1 Pencil
1 Wristwatch
1 Portable scale
Laptop
1 JAMAR dynamometer
1 Stopwatch
1 Tape measure
1 Pocket Talker (very helpful for hearing impaired participants)
Masking tape or tape of equal visibility

B. Preparation

On the day of the scheduled Heart Study visit it is best to call the participant or nursing home to confirm the appointment. Instruct the participant that he/she should wear a top that easily opens in the front to facilitate the ECG and remind them to have any available medications they take. With their confirmation letter, a form is included that helps to summarize their medical history since their last exam. Ask them to have this form ready.

When calling a nursing home inform the nurse that access to their patient's chart is necessary. Most nursing homes are accommodating and have the chart set aside for the visit.

Medical History

The date of the participant's last exam and the date of the participant's last health history update will be copied. The medical history taken from the participant is an update from the Heart Study's last contact with the participant (based on the date of the last Health History Update or last examination). The examiner should also refer to the Summary of Findings form in the participant's chart to verify whether a medical encounter is new or has already been identified. This form records the outcome of all Endpoint reviews and therefore documents all cardiovascular disease events adjudicated by the study.

The health status page may have incomplete data on medical encounters. Be sure to clarify any missing information and record it under medical encounters on the first screen of the medical history form.

Medical History Form

1st Examiner Prefix

(0=MD, 1=Tech, for OFFSITE visit)
Note: zero is in as a default, for OFFSITE visits, slash the zero out and write in 1 for Tech

Hospitalization in interim

A hospitalization is considered an overnight stay.
If the participant was in the Emergency Room (E.R.) and then admitted, the event would be considered only for hospitalization and not as E.R. visit.

E.R. visit in interim

An emergency room visit is when the person is both admitted to and discharged from the emergency room the same day.

Day surgery in interim

Day surgery is a surgical procedure performed on an out-patient basis either in an ambulatory surgery department of a hospital or in a physician's office.
The person is in and out the same day.

Major illness with visit to the doctor in interim

Illness with visit to physician is defined as a visit outside of a regular check-up. It can be further clarified by defining it as a visit to the doctor for a specific reason. It is imperative that the reason for the visit be documented.

Check-up in interim by doctor

A check-up is considered to be a routine visit.

Details of all hospitalizations, ER visits, day surgery, and physician visits must be provided as follows:

A. Medical Encounter
Write the details about the medical event. If the participant cannot provide a "medical condition", symptoms leading to the medical encounter should be listed (for example, chest pain, shortness of breath).

B. Month/Year
Record the date of the medical encounter. People often cannot recall the exact month or even the year. Trying to couple the event with a season or holiday sometimes helps.

C. Site of the hospital or office
The hospital and the city and state are most important.

D. Doctor
Record the name of the physician seen. If the participant sees a physician's assistant or a nurse practitioner in the physician's office, obtain both names.

Note: If FHS needs outside hospital records, please obtain details: mo/yr, hospital site.

Medical History – Prescription and Non-Prescription Medication

On home visits, the participant is asked to show the FHS staff his/her medication bottles including over-the counter preparations. The FHS staff takes a picture of the medication on their tablet. In the case of a nursing home visit, the technician should record the medications from the participant's medication orders in their nursing home chart.

Take a picture of the name of the medication, the strength including units, and the total number of doses per day/week/month. Include pills, skin patches, eye drops, creams, salves, injections. Include herbal, alternative, and soy-based preparations.

Make sure the medication name, strength, number per day/week/month, and if taken PRN is shown clearly on the picture.

*****List ONLY medications taken regularly in the past month/ongoing medications*****

Medical History

The physician/NP will obtain an interim medical history using the Exam 10 RedCap form. The questions should be asked exactly as written on the form and the participant's response recorded according to the response choices provided on the form. In addition a comment area is provided on the form to record a narrative account of cardiovascular symptoms including chest pain, shortness of breath, syncope, exertional leg discomfort and cerebrovascular symptoms. It is critical that a narrative be provided to clarify the symptoms for investigators adjudicating events in Endpoint Review.

It is also critical to record all health care visits (physician, ER, hospital) the participant has had for the symptom. Outside medical records will be obtained to verify the participant's account of their medical condition.

Additional instructions for obtaining the medical history and properly coding the participant's responses are as follows.

Chest pain (screen MD13)

When the participant states that they have not experienced any chest discomfort, clarify further using the terms *chest pain, chest tightness, chest pressure*.

If the participant states that they never used Nitroglycerin as a way to relieve the discomfort be sure to code as 8= not tried, rather than 0= no relief.

Alcohol Consumption (screen MD09)

Code number of alcoholic beverages as EITHER weekly **OR** monthly as appropriate.

Cerebrovascular, Neurological and Venous Diseases (screen MD15)

It is important to stress that these CVA symptoms are **sudden**, not a gradual progression of a symptom.

1. Sudden Muscular Weakness
   *Since (date of last FHS exam) until today, have you experienced any **sudden** muscular weakness? For example, face drooping or weakness, particularly on one side of your body.*

2. Sudden Speech Difficulty
   *Since (date of last FHS exam) until today, have you experienced any **sudden** difficulty with your speech such as understanding spoken words or trouble speaking?*

3. Sudden Visual Defect
   *Since (date of last FHS exam) until today, have you experienced any **sudden** visual defect?*

4. Sudden Double Vision
Since (date of last FHS exam) until today, have you experienced any double vision?

5. Sudden Loss of Vision in One Eye
*Since (date of last FHS exam) until today, have you experienced any **sudden** loss of vision in one eye, like a shade coming down over your eye?*

6. Sudden Numbness, Tingling
Since (date of last FHS exam) until today, have you experienced any numbness or tingling on one side of your face or one side of your body?

If the participant answers yes, ask is numbness and tingling positional?

CVD Procedures (screen MD17)
The participant is queried regarding CVD procedures since the last Heart Study contact.
If the participant has had more than one procedure of a particular type code only the first procedure and list all other procedures in the comment section.

Clarify the procedure list for the participant as follows:

Heart valvular surgery
Have you had surgery on your heart valves?

Exercise tolerance test
Have you had an exercise stress test or a treadmill test of your heart?

Coronary Arteriogram
This test is an invasive test done in the hospital. An x-ray is taken of your arteries after you receive an injection of a dye that outlines the blood vessels of your heart.

Coronary artery angioplasty/stent/PCI
Angioplasty is a procedure in which a balloon is used to open a narrowed or blocked artery in your heart. (This is also known as Percutaneous Coronary Intervention (PCI)). A stent is a wire mesh tube that is placed in the artery to hold it open. The stent is usually placed in the artery during angioplasty.

Coronary bypass surgery
Have you had bypass surgery also known as CABG (coronary artery bypass grafting)? During bypass surgery the diseased section of your coronary arteries are bypassed with a healthy artery or a vein in order to increase blood flow to your heart muscle.

Permanent pacemaker insertion
Have you had a pacemaker inserted? A pacemaker is used to replace the function of the natural pacemaker in your heart when your heart is beating too slowly. Permanent pacemakers are surgically placed into the chest through a small incision.

AICD
This stands for Automatic Implantable Cardiac Defibrillator (AICD) and is a device that is implanted under the skin of the chest to analyze the rhythm of your heart and discharges an electrical shock if a serious irregularity is detected.

Carotid artery surgery/stent
The carotid artery is located in your neck and carries blood and oxygen to your brain. Carotid artery surgery is a surgical procedure to restore adequate blood flow to your brain. A stent is inserted into the carotid artery to open a narrowed or blocked area of the artery to help maintain an adequate blood flow to the brain.

Thoracic aorta surgery
Have you had surgery on your aorta- the large blood vessel coming from your heart? This surgery is done to repair the aorta for example when there is an aneurysm (a weaknening or bulge in the wall of the aorta) .

Abdominal aorta surgery/stent
Have you had surgery on the large blood vessel in your abdomen (belly) called the aorta? This surgery would be done to repair a problem such as an aneurysm (weakening or bulge in the wall of the artery) or blockage in the aorta.

Femoral or lower extremity surgery/stent/angioplasty
Have you had any surgery to improve the circulation in your legs such as bypass surgery or angioplasty?

Lower extremity amputation
Have you had an amputation of part of your leg or foot?

Other cardiovascular procedures (write in)
Have you had any other tests or procedures on your heart or blood vessels?

Nursing Home Chart Review Protocol

When visiting a participant in a Nursing Home most of the necessary information may be obtained through the review of the participants Nursing Home chart. When calling to confirm the offsite visit to the Nursing Home, inform the nurse taking care of the participant that you will need to look through his or her chart. Most nurses will ensure that the chart will be available upon your arrival.

1. Updating Sociodemographic Data and Family History

   Upon opening the nursing home chart, one should see a face sheet. This sheet contains all the personal demographic data on their patient, including their next of kin. If the name(s) vary from the most recent ones on the Personal and Family History it should be documented, along with their addresses and phone numbers.

   At the bottom of the face sheet it often lists the admission diagnosis of the patient. This is extremely important, especially if this is their first Nursing Home offsite visit.

2. Medications

   Most charts contain an up-to-date list of the patient's medications. Some facilities keep the medications in a separate chart. If the patient's medications are not listed in their chart, ask for the medication book. Many times the medication sheets for months prior may also still be in the chart, make sure you use the most recent medication list (the dates will be at the bottom of the form).

3. Interim Medical History

   The two sections that are most helpful in locating medical history information are "Consults" and "Medical History". Some nursing homes keep copies of all hospitalization records in a clear sleeve. The "Physician's Notes" and "Nurses Notes" sections are also helpful.

   NOTE: Since all facilities have their own chart organization system it is best to thoroughly examine the whole chart. Some facilities thin their charts more frequently and if only the last month's information is present, then ask to see the whole interim period. This will ensure that nothing is missed.

4. Activities of Daily Living

   To update a participant's activities of daily living the best reference is the MDI or minimum data sheet. This is a computer sheet, usually at the front of the chart, and it is updated about every 4 to 6 months. This sheet lists activities of daily living, hospitalizations, etc. Always refer back to notes and daily documented information to corroborate data, but this gives a nice head start. To truly confirm the current level of functioning of the patient consult with his or her nurse and list nurse as the Proxy.

5. Weight

   If you are unable to obtain the participants weight using the FHS protocol you can use their nursing home chart records. Weight is typically done weekly at nursing home facilities. If you can't find a list of their current weight you can reference their physical exam report. Check to see if the nursing home keeps a separate weight book first before using the physical, we want to use the most recent measurement. Record the weight on file and the date it was obtained.

Visiting the Cognitively Impaired

The physical component of the exam requires the cooperation of the participant. The following are some suggestions to be able to effectively communicate with those with dementia.

Effective Communication Suggestions:

1. Be patient
2. Do not try to reason
3. Keep information simple
4. Use given names
5. Use eye contact
6. Give one direction at a time
7. Give clear instructions instead of asking questions
8. Keep communication in the present
9. Use sensitive touch when possible
10. Give frequent acknowledgment and encouragement
11. Ignore misinformation and simply acknowledge the communication

Offsite Visit Chart Completion

After returning to the Heart Study the following procedure is used to ensure that the chart is processed in an efficient manner.

A. ECG Physician Review

The full size tracing of the ECG and the ECG from the participant's previous exam should be presented to a FHS Nurse Practitioner within 24 hours of the visit or within 24 hours of the tech returning to the FHS (if the Nurse Practitioner is not at the Offsite visit). This is done for comparison and reading. Should there be any marked ECG changes; the FHS Nurse Practitioner should inform the participant's personal physician immediately.

After a contact is made with the PCP, the Nurse Practitioner should complete a phone encounter sheet or the referral tracking form to document his/her actions.

The field visit tech/NP will complete the chart/REDCap the day of the visit or the next day if the visit occurred late in the day or was out of the Metrowest area.

B. Chart Review Protocol

1. Review all forms in RedCAP to ensure that all areas are completed. This includes the participant's letter and the physician summary sheet. On the summary sheet, document the medical findings that are new since the last exam and any other significant medical conditions carried over from previous exams.

2. If the participant had a stroke or has shown marked cognitive changes in the interim, a referral is made to the Stroke and/or Dementia study. After completing the referral forms, attach to the front of the chart.

Weight Offsite Visits

1. The participant should remove slippers or shoes.

2. Prior to asking participant to step on the scale, turn scale on, check to make sure it reads 0.0. The scale should be on a flat, hard surface.

3. Ask the participant to step onto the scale.

4. Instruct the participant to stand in the middle of the scale platform with head erect and eyes looking straight ahead. Weight should be equally distributed on both feet, and participant should not touch or support himself/herself.

5. Read the digital display while participant is on the scale.

6. Have the participant step off the scale.

7. Record the weight to the nearest pound; round up if ≥ 0.5, round down if < 0.5.

9. If participant is unable to stand for weight measurement at a nursing home, record the last weight in nursing home chart and the date the weight was obtained. If the participant is unable to stand on a scale during a home visit, record the weight measurement as 999.

10. Calibrate the scale monthly with 50lb weight

Overview

- Research studies that involve imaging may lead to incidental discovery of clinically relevant findings
- Different NHLBI sponsored cohort studies have historically managed these issues in different ways, but with a common theme: *verify, prioritize, then communicate*
- NHLBI approved a process for managing incidental findings in the HCHS-SOL (Study of Latinos) Echo multi-site study, wherein there was a high level of concern for ensuring communication back to a population of participants (Hispanics/Latinos) who are especially vulnerable to gaps in clinical care; this approach was thus more inclusive than most others
- Nonetheless, the general approach may be adopted for FHS and other NHLBI sponsored studies, with tailoring as needed

SOL Echo approach

- The SOL approach covered…
- What to do if a sonographer discovered an incidental finding in real time (most common scenario)
- What to do if the central reading center discovered an incidental finding weeks later (less common scenario)
- How findings are communicated to the participant: in-person and via letter

SOL Sonographer identifies an abnormality

- At Field Center
- In Real-Time

- At Reading Center (Boston, MA)
- Anticipate ~ 4 – 6 week lag

- Summary Letter (several months)

Sonographer performing the echocardiogram → Echo Research Specialists performing quantitative assessment of echo → Cardiologist Over-reader reviews study → CC (UNC)

Identifies a critical abnormality

Alerts site investigator directly

Site investigator is responsible for handling alert findings (as alerts requiring emergency or immediate referral, urgent referral, or routine referral as appropriate), incl discussing with dedicated off-site local cardiologists (who can review images remotely via TeamViewer), relaying findings to participant and, where consent provided, to treating provider

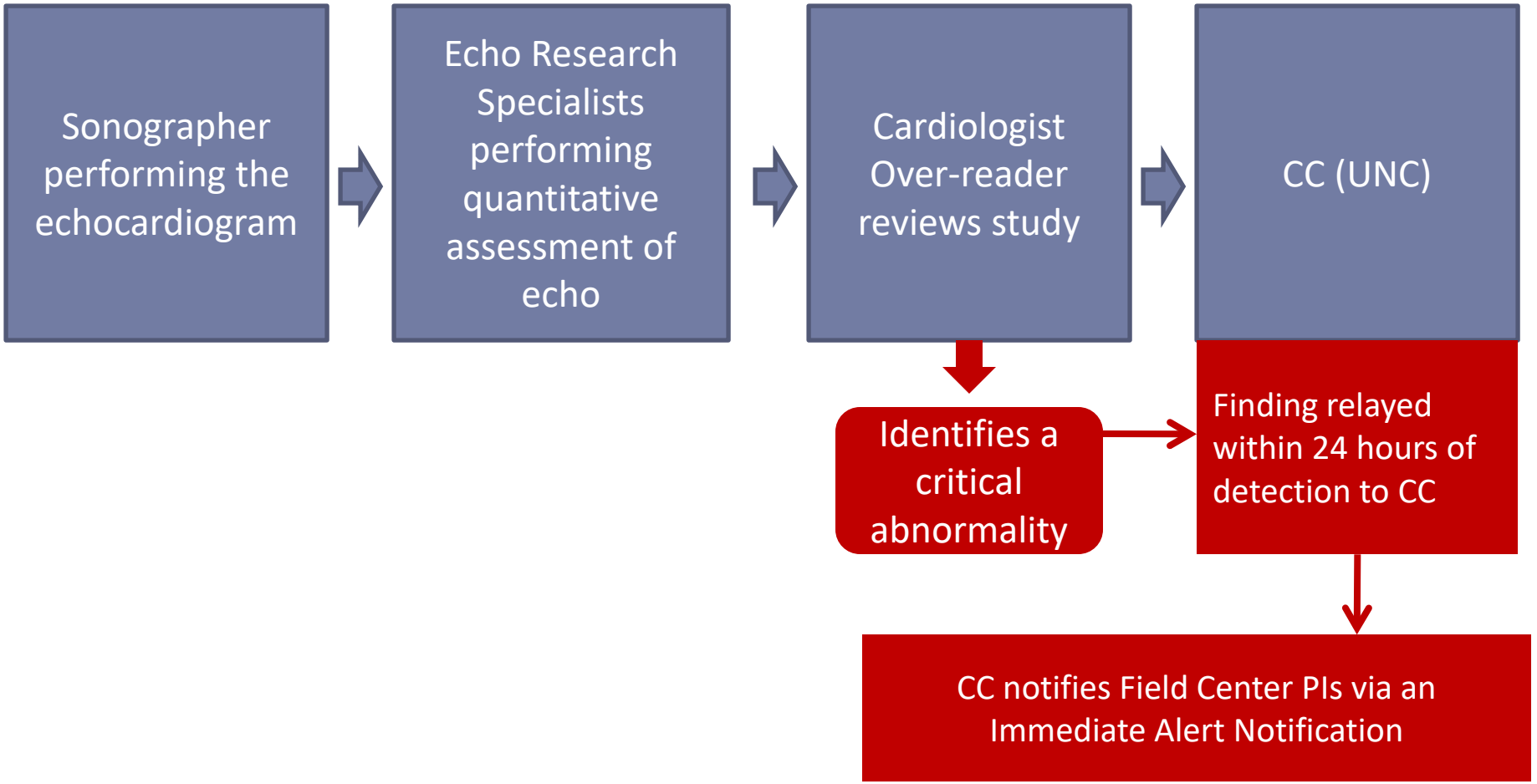
Inform Reading Center via eCRF – facilitate an expedited analysis of that study

Reading Center identifies an abnormality

- At Field Center
- In Real-Time

- At Reading Center (Boston, MA)
- Anticipate ~ 4 – 6 week lag

- Summary Letter (several months)



Final reports are sent to all participants with or without extra comments regarding potential abnormalities

ECHOCARDIOGRAPHY (ECHO)

An echocardiogram is a cardiac ultrasound that measures cardiac structure and function. During this HCHS/SOL visit, participants 45 years of age or older may have an echocardiography examination.

The echocardiogram that you had performed was for research purposes only and is not as extensive as a clinical echocardiogram. This echocardiogram was analyzed in the absence of any clinical information, and is not meant to substitute for a clinical echocardiogram.

Your Cardiac Echo Results

Measurement	Value	Brief Interpretation
LV ejection fraction(%)	37.2	Your echocardiogram showed moderately reduced heart function. These findings should be discussed with your physician and follow-up clinical studies may be warranted.
LV diastolic diameter (cm)	4.8	Within normal limits.
LV wall thickness (cm)	0.6	Within normal limits.

Your echocardiogram showed

- There is echobrightness seen in the left ventricular apex that likely represents simply an imaging artifact rather than a thrombus or mass.

These findings should be discussed with your physician and follow-up clinical studies may be warranted.

*Ad hoc p*reliminary letters are sent earlier (prior to the final reports being made available), on an as needed basis

[date]

Dear Mr. or Ms. [name]:

Thank you very much for your ongoing participation in the SOL study, and particularly for your contribution to SOL visit 2. During SOL visit 2, we performed an ultrasound scan of your heart (i.e. echocardiogram).

The echocardiogram that you had performed was for research purposes only and is not as extensive as a clinical echocardiogram. This echocardiogram was analyzed in the absence of any clinical information, and is not meant to substitute for a clinical echocardiogram. The assessments below of cardiac structure and function are being provided as a courtesy, along with reference ranges.

Parameter	Your Value	Reference Ranges				
		Sex	Low Normal	Mildly Abnormal	Moderately Abnormal	Severely Abnormal
LV ejection fraction (%)	**64**	Both	50 – 54	45 – 49	30 – 44	<30
LV diastolic diameter (cm)	**4.1**	Men		6.0-6.3	6.4-6.8	≥6.9
		Women		5.4-5.7	5.8-6.1	≥6.2
LV wall thickness (cm)	**1.0**	Men		1.1-1.3	1.4-1.6	≥1.7
		Women		1.0-1.2	1.3-1.5	≥1.6

These findings could be further evaluated with a clinical echocardiogram, ordered by your own doctor, if clinically indicated. In addition to the measurements listed above, SOL physicians reviewed the images and provided the following additional comments:

There appears to be mitral valve prolapse and at least moderate and possibly severe mitral regurgitation. Recommend clinical evaluation with a cardiologist.

Because the SOL echocardiogram was performed for research and not clinical purposes, we recommend that you follow up with your doctor at your earliest convenience to see if she or he would like to evaluate your heart function further.

If you have any questions about this letter, please feel free to contact me.

Sincerely,

[Site PI name, degree]

SOL Site Principal Investigator

A list of ‘critical findings’ is clarified up front

- Potentially serious abnormalities that may require urgent/emergent medical evaluation
- Include, but are not limited to:
  1. Tamponade
  2. Aortic dissection
  3. Thrombosed or frankly dysfunctional prosthetic valve
  4. Pseudoaneurysm
  5. Intracardiac abscess or obvious vegetation
  6. Intracardiac thrombus

HCHS/SOL Echocardiography Alerts Notification for Visit 2

ID NUMBER:								

FORM CODE: ECA
VERSION: 1
10/202014

Contact Occasion: 0 2 SEQ #: 0 1

ADMINISTRATIVE INFORMATION

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

0b. Staff ID: BWH-CICL ☐☐☐

Instructions: *This form is completed by the Echocardiography Reading Center to document critical results noted during the over-read of the echocardiogram. If the HCHS/SOL echocardiogram is judged to have a condition that would require emergent notification, an echocardiography alerts notification form is completed. An alert report is auto-generated for the field centers once a notification is entered into the Data Management System.*

1. Date of echocardiogram at the field center ..... ☐☐/☐☐/☐☐☐☐ (M M D D Y Y Y Y)

2. Date of receipt of the echocardiogram ..... ☐☐/☐☐/☐☐☐☐ (M M D D Y Y Y Y)

3. Critical results noted from the echocardiogram:

Condition (check all that apply)	Yes	No
Tamponade	☐	☐
Aortic dissection	☐	☐
Thrombosed or frankly dysfunctional prosthetic valve	☐	☐
Pseudoaneurysm	☐	☐
Intracardiac abscess or obvious vegetation	☐	☐
Intracardiac thrombus	☐	☐
Other (specify: _____)	☐	☐

4. Date of reading ..... ☐☐/☐☐/☐☐☐☐ (M M D D Y Y Y Y)

5. Code number of the preliminary grader ..... ☐☐☐

A. CRITICAL ALERTS

Abnormalities that would trigger a critical result include, but are not limited to:

- tamponade
- aortic dissection
- thrombosed or frankly dysfunctional prosthetic valve
- pseudoaneurysm
- intracardiac abscess or obvious vegetation
- intracardiac thrombus

other: ventricular septal defect, intracardiac mass/tumor

B. NON-CRITICAL ALERTS

Abnormalities that are not a critical alert but will be expedited for review:

- low EF <=30%
- pericardial effusion > 1cm, without hemodynamic compromise
- flail MV leaflet with severe MR
- other severe valvular disease (aortic, mitral, tricuspid, or pulmonic)
- hypertrophic cardiomyopathy with evidence of obstruction
- severe pulmonary HTN with PASP >70 mmHg
- large aortic aneurysm with ascending aorta >50 mm diameter
- complex congenital heart disease

C. OTHER ABNORMALITIES

Other abnormalities, not listed above, may be seen on echo and are not generally considered to be in need of urgent attention. If you have questions about other abnormalities not listed above, please feel free to contact the central Echocardiograph Reading Center at any time: echocore@rics.bwh.harvard.edu and (617) 525-6730.

FHS Echo and Vascular Approach

- The FHS approach to echo and vascular findings can be similar to that of SOL, but also streamlined because the field center and reading center are the same (single site study)
- Whether an incidental finding is discovered in real time (most common scenario) or days/weeks later while doing measurements or overreading (less common scenario), the same protocol can be applied
  - Verify: if finding is not obvious, sonographers can review with cardiologist/attending (via secure TeamViewer or Zoom, if attending is CITI certified and on a relevant IRB)
  - Prioritize: as critical vs. non-critical (see SOL list for criteria); all other findings can go into a final report but do not need to be communicated in any expedited fashion
  - Communicate: to participant within days to weeks (depending on priority level); if high priority, can ask participant for permission to also communicate directly with their primary physician
- Findings are communicated to the participant:
  - Critical or non-critical findings communicated in-person (or by phone), and
  - via letter (so there is documentation that can be provided to a treating physician, and/or just kept for reference)
- Communication of findings is documented in RedCap

FHS Echo and Vascular Approach

Echo Alerts

A. CRITICAL ALERTS

Abnormalities that would trigger a critical result include, but are not limited to:

- tamponade
- aortic dissection
- thrombosed or frankly dysfunctional prosthetic valve
- pseudoaneurysm
- intracardiac abscess or obvious vegetation
- intracardiac thrombus

other: ventricular septal defect, intracardiac mass/tumor

B. NON-CRITICAL ALERTS

Abnormalities that are not a critical alert but will be expedited for review:

- low EF <=30%
- pericardial effusion > 1cm, without hemodynamic compromise
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- other severe valvular disease (aortic, mitral, tricuspid, or pulmonic)
- hypertrophic cardiomyopathy with evidence of obstruction
- severe pulmonary HTN with PASP >70 mmHg
- large aortic aneurysm with ascending aorta >50 mm diameter
- complex congenital heart disease

C. OTHER ABNORMALITIES

Other abnormalities, not listed above, may be seen on echo and are not generally considered to be in need of urgent attention. If you have questions about other abnormalities not listed above, please feel free to contact the central Echocardiograph Reading Center at any time: echocore@rics.bwh.harvard.edu and (617) 525-6730.

Vascular Alerts

A. CRITICAL ALERTS

- Dissection
- Thrombus
- Aneurysm

B. NON-CRITICAL ALERTS

In order of priority for communication:

- Complete occlusion of flow
- Mass compression
- Severe stenosis (>=70%, PSV>285, EDV>85)
- Moderate stenosis (50-69%, PSV 135-284, EDV>40)
- Mild stenosis (<50%, PSV<135, EDV<40)

FHS Exam 10 Vascular Station Summary
Gary F. Mitchell, MD
October 21, 2019

1. Exam procedure
    a. See attached exam-specific flowsheets:
        i. NIHem Protocol Summary New (10.18.2019).pdf
        ii. NIHem_Flowsheet_Ton_PQ_Dias_Car_10.18.2019.pdf
2. Staff Training
    a. See attached training and operations manual: NIHem_Protocol_Long_10.21.19.pdf
3. Equipment + Equipment Calibration schedule
    a. NIHem-USB workstation, calibrated annually
    b. Philips IE33 ultrasound machine with cardiac and vascular transducers, calibrated annually
4. Quality Control and Certifications
    a. All operators will perform certification studies prior to initiation of the new exam cycle.
    b. All data is screened for quality; scores are summarized and reviewed with sonographers every 4 months (or more frequently if specific problems emerge)
5. Data Collection (RedCap, Paper, Data Entered, etc)
    a. Same tonometry checklist as per Exam 3 (retooled for REDCap)
    b. All other data is automatically saved as NIHem data files and DICOM files
6. If the study has a medically actionable result that will generate a report, please include rationale for report and report template.
    a. See attached plan: FHS Echo and Vasc alerts and R0R process V1.pptx
    b. See attached letter templates:
        i. CV scan_sample letter to PCP V3.docx
        ii. CV_scan_sample letter to participant V3.docx

Framingham Heart Study
73 Mt. Wayte Avenue, Suite 2
Framingham, MA 01702-5827
-Tel 508-935-3417

PCP Name
PCP Address

Dear Dr. XXX,

Your patient, [participant name here], participated in the recent research examination at the Framingham Heart Study. In his/her consent form, your patient gave permission to provide findings of non-genetic research tests and examinations to him/her and to you as a physician or other health care provider. We are now providing you some findings as described below.

Your patient underwent a limited heart and vascular scan done for research purposes only and analyzed in the absence of comprehensive clinical information. The results of the scan suggest that your patient may have [insert findings here]. We are informing you of these findings so that you may consider them in clinical context. If clinically indicated, you may suggest arranging for your patient to have a dedicated comprehensive clinical [echocardiogram / vascular scan] performed for further evaluation.

As a reminder, the research examination at the Heart Study is not considered clinical care and all testing is done for research purposes only. The research examination does not take the place of medical care by a physician or health care provider and cannot be relied upon to identify health conditions. Research test measurements and findings are not the same as clinical test results. As such, our research examination is not necessarily performed by individuals with clinical training and qualifications, and many parts of the examination do not meet the standards for certified clinical testing. For these reasons, our research tests should not be relied on to make any diagnosis, treatment, or health planning decisions.

Please feel free to contact us if you have any questions.

Sincerely,

[FHS physician-investigator name, degree(s)]

Cardiac and Vascular Laboratory, Framingham Heart Study

The Framingham Study's Noninvasive Cardiovascular Testing Station

In the cardiovascular testing station, you will receive two tests that noninvasively examine the structure and function of your heart and blood vessels. None of the tests involve radiation. You will receive the following tests:

1. Blood pressure

- The sonographers will carefully measure your blood pressure while listening with headphones.

2. Arterial tonometry

- The sonographer will hold a flat pressure-sensing device (the tonometer) against the superficial pulses in your elbow, wrist, top of your leg and neck for approximately a minute at each of these four sites. This approach allows us to assess blood vessel stiffness. At the very end of all vascular testing, the sonographers will measure the distances between the 4 sites where the pulse recordings were taken. **Details of the test are provided on the reverse side.**
- The sonographer will also acquire limited ultrasound pictures of the aorta (the large artery carrying blood flow from the base of your heart) and heart as part of the tonometry evaluation. This is not a clinical echocardiogram and the results will be used for research only.
- Finally, the sonographer will take limited pictures of your carotid arteries. Again, this is a very limited assessment designed to assess blood flow and hemodynamics only. This research test is not a valid screening measure for carotid artery disease and will be used for research only.
- <u>The Arterial Tonometry Test results are solely used for research purposes. They are not used in clinical practice or to guide medical decisions. For this reason, we will not be sending the results to your physician.</u>

If at any point during the testing you are uncomfortable and would like to terminate the tests, please tell the sonographers.

Thank you for your support of the research at The Framingham Study.

The Arterial Pressure Waveform Test (Tonometry)

How is the test performed?

- Measurements are made by gently pressing the side of a flat pressure sensing device (the tonometer) against the superficial pulses in the arm, leg and neck for approximately a minute at each of four sites. This device records the pressure waveform that is associated with each pulse or heartbeat.
- Next, the distance from the base of the neck to each of the pulse sites is measured.
- You will be asked to lie quietly during this phase of the testing. There should be no discomfort. This test has been performed safely in thousands of patients.
- At a later date, using a computerized analysis, we will examine the shape of the pressure waveforms and calculate the speed at which pressure waves travel through the large arteries.
- We will also measure blood flow into the aorta and carotids in order to assess the effects of arterial stiffness on the heart and brain.

Why are we doing this test?

- The arterial pressure waveform test is a noninvasive method to evaluate the stiffness of the large arteries.
- This test will allow us to evaluate the relationship between cardiac risk factors, arterial stiffening and the development of cardiovascular disease.

If you have further questions about the noninvasive tests please contact Maureen Valentino at (508) 872-6562.

FRAMINGHAM HEART STUDY

Transient Elastography

MANUAL OF PROCEDURES FOR OFFSPRING COHORT EXAMINATION 10/ OMNI COHORT EXAMINATION 5

Date: 08/22/2019

Table of contents

- ## Overview

Participants in the Offspring and Third Generation Cohorts have undergone measurement of liver fat as a part of the multi-detector computed tomography sub-studies. However, the examination of liver fat on CT is insensitive to mild liver fat and also insensitive to liver fibrosis.

All eligible participants at the Offspring Cohort/OMNI Cohort 10^{th}/5^{th} examination will be offered **vibration-controlled transient elastography (VCTE)** of the liver (FibroScan, Echosens Corporation, France). VCTE produces fast, accurate, and noninvasive measurements of liver fat and fibrosis.

- **Background**

www.myliverexam.com/en/lexamen-fibroscan.html

The FibroScan system is an active, non-implantable medical device using ultrasound.

The FibroScan system is intended to provide 50 Hz shear wave speed measurements and estimates of tissue stiffness as well as 3.5 MHz ultrasound coefficient of attenuation parameter (**CAP: Control Attenuation Parameter**) in internal structures of the body.

The FibroScan probe comprises a single-element ultrasound transducer mounted on the shaft of the electrodynamic transducer. This transducer generates a transient vibration, which in turn generates an elastic shear wave. This wave propagates through the skin, the subcutaneous tissues, and then the liver. During shear wave propagation, the ultrasound transducer performs a series of ultrasound acquisitions (emission / reception) to measure the speed of shear wave propagation (Vs) in m/s (**LSM: Liver Stiffness Measurement**). This measurement corresponds to the spatial and temporal average speed of propagation of the shear wave through the liver region of interest, which can be approximated by a cylinder with a diameter of 1 cm and a length of 4 cm (which corresponds to about 3 cm3).

In addition, assuming that the liver is a pure elastic, linear and isotropic medium, the device converts shear wave speed Vs into equivalent stiffness E in kPa using the equation $E = 3 \times \rho \times Vs2$ with ρ the medium density assumed to be 1000 kg/m3. The values for shear wave speed and equivalent stiffness (or Young's

modulus) are relative indexes intended only for the purpose of comparison with other measurements performed using FibroScan devices.

Concomitantly, the ultrasound acquisitions are used to assess the CAP. Ultrasound attenuation corresponds to the loss of energy as ultrasound propagates through the medium. Due to attenuation, the intensity of emitted ultrasound decreases exponentially with depth (z): $Iz = I0 \times \exp(- \alpha(f) \times z)$ where Iz is the ultrasound intensity at depth z, α is the frequency (f) dependent attenuation coefficient. Ultrasound attenuation depends principally on (i) the ultrasound frequency, (ii) the properties of the medium of propagation. CAP assesses the value of α at the frequency f = 3.5 MHz and is expressed in dB/m.

Absolute values for these measurements may vary among measurement devices produced from different manufacturers.

- ## Staff training requirements

Training requirements for new staff

1) Read and understand the manual of procedures.
2) Complete training certification program with Echosens representative.
3) Perform unprompted VCTE in 5 non-participant volunteers while observed by certified technician or principal investigator.
4) Perform VCTE on 5 FHS participants while supervised by certified technician or principal investigator.

- ## Subject selection for VCTE

All participants will be offered VCTE unless they meet any exclusion criteria which will be determined by the technician.

Participants will be excluded if:

a. They have active medical implants (such as pacemakers, defibrillators, pumps, etc).
b. They have a wound on their chest wall over the liver which would interfere with probe placement
c. They have significant ascites

- **VCTE Equipment and technical support contact**

  Fibroscan® 502 Touch with M^+ and XL^+ probes

Training & Clinical Applications Specialist
Echosens North America, Inc.
1050 Winter Street
Waltham, MA 02451
+1 (857) 320-7116
service@echosens.com

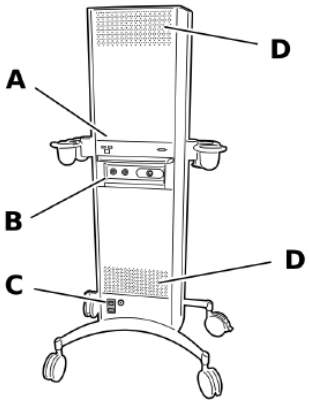
- **VCTE equipment daily procedures**

Please refer to user manual for more detailed instructions and diagrams

1) Turn on device (switch labeled “C” below).

5.4. REAR VIEW

The following figure presents the instrument's different user-accessible parts.



***Rear view:** **A:** Computer sockets. **B:** Probe sockets. **C:** Power connector. **D:** Perforated ventilation plates.*

2) Clean each probe (see user manual section 8 and instructions below from user manual).

It is not necessary to switch off the device before cleaning the probe.

Surfaces must be cleaned in strict compliance with the following procedures:

1. Gently remove the gel using a soft cloth or wipe.

Cleaning the probe: A: *Wipe.*

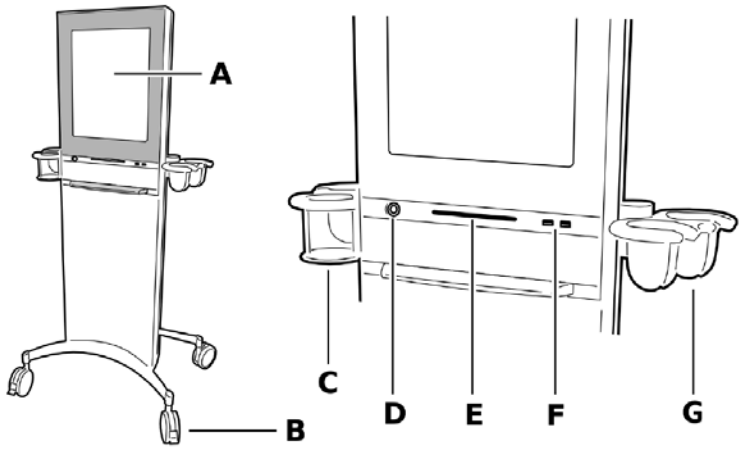
2. Remove all traces of bodily fluid by cleaning the surfaces using a soft cloth or wipe soaked in the recommended cleaning product.
3. If necessary, rinse the cleaned surfaces using a soft cloth soaked in water.
4. Dry, if necessary, using a dry cloth.
5. Wipe the surfaces using a soft cloth or wipe soaked in the recommended decontamination solution.
6. Dry, if necessary, using a soft dry cloth.
7. Examine the transducer and probe cable for any damage such as cracks, breakage, or liquid leakage.

3) Change file transfer setting to “Data Anonymization – Disabled”
   a) Choose Fibroscan –Administrator
   b) Put in admin password: 5UP374DM1N
   c) Select wrench on the bottom of the screen
   d) Re-enter admin password: 5UP374DM1N
   e) Touch the “connectivity icon”
   f) Choose directory
   g) Change “Data Anonymization” to Disabled
   h) Choose Apply
   i) Exit administrative mode
   j) NOTE: This must be done any time the machine is turned off or put into standby

4) Date the participant list to serve as the log page for the day.

5) Record any/all comments if issues arise or if participant refuses test or has to stop test.
   a) Record if FibroScan preformed before or after CPET
   b) Note any food eaten and the time of ingestion
   c) Note any contraindications

6) Between sessions, turn the machine off by pressing the standby button on the bottom left hand corner of the monitor (see label “D” below).



General arrangement of the FibroScan: ***A:*** *Touch screen.* ***B:*** *Caster with brake.* ***C:*** *Gel holder.* ***D:*** *Standby button with power indicator.* ***E:*** *CD-ROM / DVD-ROM drive.* ***F:*** *Computer sockets.* ***G:*** *Probe holder.*

7) After testing is complete for the day, save data for each participant onto secure thumb drive (see user manual section 6.7).

8) Upload new data to secure server.

9) Clean each probe (see user manual section 8).

10) Press the standby button to turn off the FibroScan and cut the power supply by setting the main switch to 0.

- **VCTE equipment calibration protocol**

The FibroScan devices will be sequentially calibrated on a yearly basis by Echosens.

When an exam is opened, a window displays the expiry of the calibration of the probe. When this is displayed, the technician or principal investigator will contact Echosens to arrange calibration (service@echosens.com).

- **Participant testing – detailed procedures**

a. Exclusion criteria

Prior to all tests, the technician must ask the participant about VCTE exclusion criteria:

- Ask: Do you have any implanted medical devices such as a pacemaker? If the device is active, do not perform VCTE.

- Ask: Do you have any wounds or bandages on your chest or abdomen? If yes, determine if the location is over the liver. If any skin defect would interfere with placement of the VCTE probe or patient comfort during the test, do not perform VCTE.

- Ask: Have you been told you have any problems with your liver by your doctor? If the participant answers yes to this question the technician will ask what the underlying liver problem is and make a note of this on their exam. The technician will then ask if the participant has been told that they have excess fluid in their abdomen, called ascites. If yes, the technician will determine if the participant has a large amount of ascites which would interfere with the measurement. If significant ascites is present, the technician will not perform VCTE.

- Ask: Have you had anything to eat or drink today? If yes, note what was eaten and the approximate time it was eaten (or how many hours or minutes previously). Ideally the participant has fasted for at least 2 hours prior to the examination and any snacks will be noted.

(To be placed in VCTE testing room)

VCTE EXCLUSION CRITERIA

■ DO YOU HAVE ANY IMPLANTED MEDICAL DEVICES SUCH AS A PACEMAKER?

■ DO YOU HAVE ANY WOUNDS OR BANDAGES ON YOUR CHEST OR ABDOMEN?

■ HAS YOUR DOCTOR TOLD YOU ABOUT ANY PROBLEMS WITH YOUR LIVER?

■ HAVE YOU EATEN ANYTHING TODAY?

b. Description of VCTE test

The technician will describe the test to all eligible participants. A detailed script for the description of the test is included below.

“We are asking you to participate in a study that will take measurements of your liver using a device called “transient elastography or FibroScan”. This device measures the stiffness of the liver and the amount of fat in the liver. Investigators believe liver stiffness and fat may be related to heart disease. If you choose to participate, we will ask that you lie on your back while we use a probe placed on the skin over your liver to take 10 measurements of the liver. The test is painless, but you will feel pressure from the probe during the test. We expect the test to take about 5-10 minutes.”

c. Entering participant information

Note: The FHS reference ID will be entered per participant in the “code” box (see picture below from user manual). The participant name and gender will also be entered. The Tech ID will be entered under “Operator”.

Please see section 6 of the user manual for detailed procedure.

6.5. THE PATIENT RECORD SCREEN

If the patient exists in the patient list, the data will be displayed automatically after the name is entered. Select the patient.

Complete the fields. At least the 'Name' or 'Code' field must be filled in to start the examination.

CAP — Enables/disables the CAP option for the exam about to start.

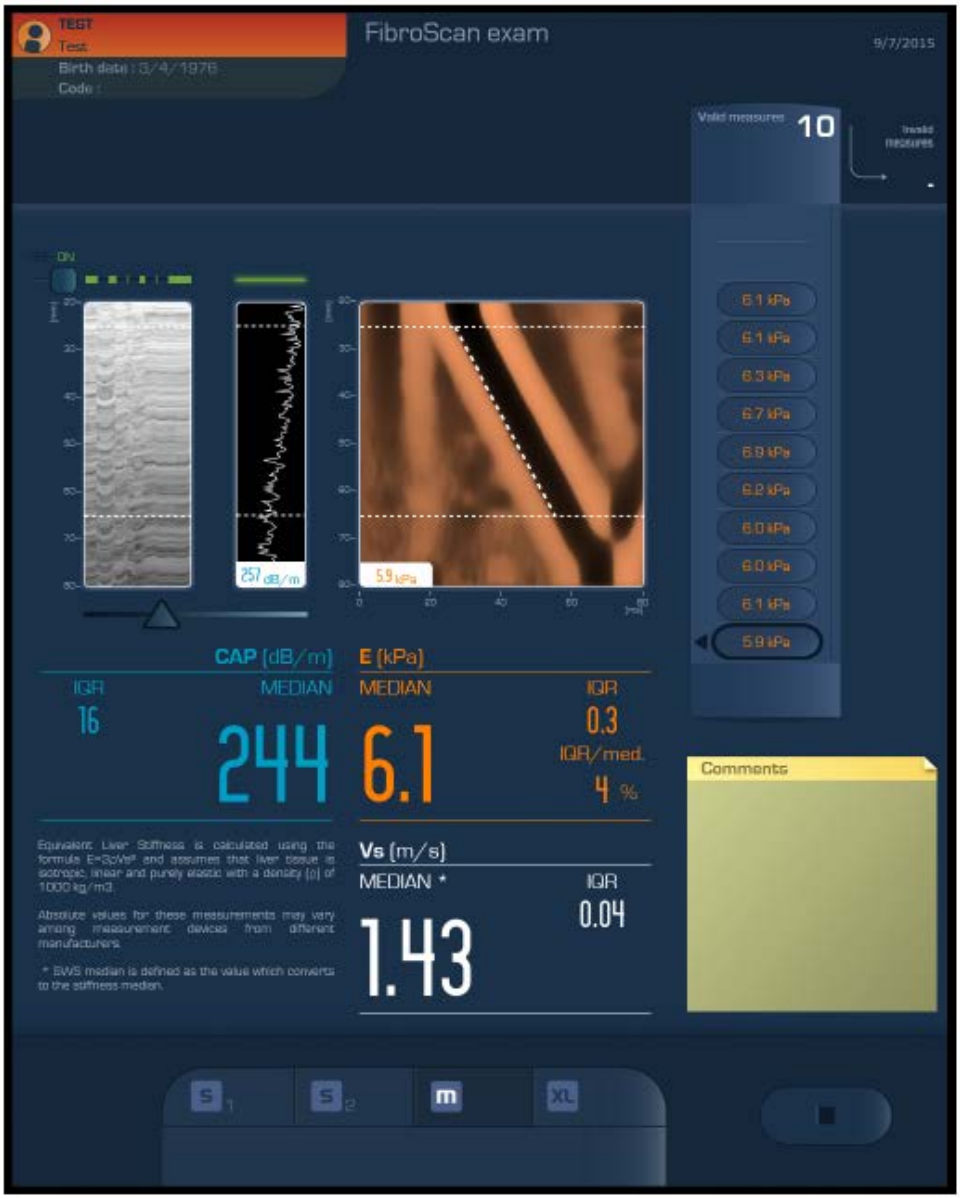
Raw — Enables/disables the saving of Raw Data for the exam about to start (available only if Clinical Mode was enabled in the Configuration).

d. Performing VCTE

Please see the user manual for detailed instructions (section 6). A picture of the acquisition screen is displayed below:

6.6. ACQUISITION SCREEN

The main data displayed in an acquisition window are presented below.



The technician will position the participant on the examination table with the FibroScan device on the right side of the participant. Participant will cross right leg over left ankle, and place right arm above head. The M^+ probe will be used as the default probe for all examinations. A small amount of gel will be placed on the tip of the probe and the probe will be positioned over the liver. Upon contacting the participant's skin, the automatic probe selection tool will begin determining the proper probe for the examination. The results of the automatic probe

selection tool will be displaced on the bottom of the screen and may be one of the following three cases:

1. Recommended probe: in progress: the tool cannot currently measure the SCD because the probe is not correctly positioned in front of the liver and/or the ultrasound signals are of poor quality.

2. ‘Recommended probe: The tool measures a SCD that justifies the use of the M+ probe. The box containing the M exam type icon flashes.

3. ‘Recommended probe: XL: The tool measures a SCD that justifies the use of the XL+ probe. The box containing the XL exam type icon flashes.

If the tool is able to recommend a probe (case 2 or 3), two situations are possible:

The probe being used matches the recommendation: the operator continues the exam without changing probes and, if he/she wishes, can confirm the probe choice by pressing the icon of the exam type concerned. The probe recommendation tool is then disabled until the end of the current exam.
The probe being used does not match the recommendation: the operator replaces the probe as explained below.

To change the probe during an exam:
1. Select the new probe type. The following message is displayed:
Change of exam type. Changing exam type causes all previous measurements to be definitively erased.
2. Click OK (warning: all measurements taken using the previous probe will be deleted), the following message is displayed: Exam type has changed. Plug the appropriate probe to continue.
3. Plug the appropriate probe if necessary and resume the exam.

After the proper probe is selected, the technician will check the liver targeting tool on the acquisition screen. The color ranges from black (quality of the ultrasound signal is low) to green (quality of the ultrasound signal is high). The greener the color of the liver indicator, the higher the quality, and the better the position of the measurement. Next the technician will check the pressure indicator. When the correct pressure is applied, the indicator will be green. If pressure is too low, the indicator will be orange and if pressure is too much the indicator is red. The measurements cannot be taken if the pressure indicator is not green.

When a measurement is complete, the shear wave propagation map is automatically displayed on the acquisition screen. It represents the levels of liver deformation generated by the propagation of the shear wave as a function of time (horizontal axis in milliseconds) and depth (vertical axis in millimeters). The

shear wave speed value is displayed if the measurement is valid. The color scale indicates the sign of the deformations (compression or expansion). Black areas correspond to negative deformation and pale areas to positive deformation. The black strip through the image represents deformations associated with the passage of the shear wave, which penetrates progressively deeper with time. Invalid measures are automatically rejected by the algorithm if the pulse sent out by the transducer could not be delivered successfully and/or if the shear wave propagation maps are not satisfactory. The message “INVALID” will be displayed above the shear wave propagation map.

Median:
Shear wave speed is expressed in meters per second (m/s), liver stiffness is expressed in kilopascals (kPa) and Control Attenuation Parameter (CAP) is expressed as decibels per meter (dB/m). These values are the median of all valid measurements performed during the examination. CAP is only calculated with the liver stiffness is valid.

If the repeat measurement is invalid, the median is not re-computed. To obtain a reliable and representative liver shear wave speed and liver stiffness measurement, **at least ten valid measurements should be made**.

Interquartile Range (IQR):
The interquartile range (IQR) is expressed in meters per second (m/s), kilopascals (kPa), or decibels (dB/m). It represents the interval around the median within which will fall 50% of all valid measurements. It is recomputed after each new valid measurement.

IQR/Median:
This value, expressed as a percentage, is the ratio of the IQR to the median stiffness. It is re-computed after each new valid measurement. **The goal will be to have the IQR/Median ≤ 30% which indicates a high quality examination.**

If the IQR/Median is > 30% or if a liver stiffness measurement is clearly spurious, the measure can be deleted. The technician will press the measurement to be deleted on the touch screen and press the “X” button to delete. A confirmation request is displayed and indicates the number of measurements if deletion is confirmed. The technician can then continue to take measurements to get to a total of 10.

e. Data procedures after participant testing

- After each examination, the technician will note if any criteria for results reporting are met (see section 10. Results reporting) and will alert the study PI (Michelle Long, MD).

- At the end of the day, all results for that day need to be exported to a removable USB storage device in .XLS format.
- The .XLS file will be transferred to the folder \\fhs-svr-filserv\Fibroscan on a daily basis.

Log book: All participants are entered into the "VCTE daily log and comments" binder (including those that have not had a VCTE done so that the reason can be noted). The participant list for the day will serve as the log page. The technician will record any issues with the VCTE as noted below:

|__|	**VCTE**		0=Not Done, 1=Done, 2=Attempted, not finished, 3= Attempted, tech aborted ,4=Other
	|__|	**Reason VCTE not done**	1=Medical exclusion, 2=Refused, 3=equipment problems 4=Other

- Quality control

Every three months, the PI (Michelle Long, MD) will observe each technician perform transient elastography on a participant. Constructive feedback will be provided as warranted.

The liver stiffness measurements (LSM) and controlled attenuation parameter (CAP) measurements obtained from participants will be evaluated quarterly. We will review age-, sex-, and body mass index-adjusted averages of the LSM and CAP values during the study interval and compare to the prior interval and expected values. We will stratify by whether or not the FibroScan was performed before or after the cardiopulmonary exercise testing station.

A second technician will be trained in VCTE and perform a minimum of 1 scan per week. We will measure intra-operator (repeated VCTE on same participant using the same operator and probe) and inter-operator (repeated VCTE on same participante using the same probe but a different operator) agreement on 50 participants yearly.

- Results reporting

The FibroScan device measures both liver fibrosis and liver fat. Liver fibrosis may be clinically significant and may warrant additional testing. For this reason, we will report to the participant and their primary care doctor if the liver stiffness measurement (LSM) is ≥ 8.0 KPa which may indicate significant fibrosis of the liver.

Specific procedure:

Technician: The technician will review the results of the LSM obtained from each participant. If the LSM is ≥ 8.0 KPa the technician will call the Principal Investigator (Michelle T. Long, MD) at 617-638-8392 and email at mtlong@bu.edu. After discussion with the principal investigator, the technician will generate the participant letter and letter to the primary care doctor (see below).

Principal Investigator: The principal investigator will review all the results from the participant examinations at least once per month. Any participant with an LSM ≥ 8.0 KPa will receive a letter along with other results from the FHS (as specified by the core exam and other ancillary study results reporting mechanisms). The primary care doctor will be alerted in the form of a letter as well (sent along with other FHS results).

A copy of the result letter will also be placed in the participant's chart.

Sample letter to participant:

"Dear FHS participant:

At the Framingham Hearst Study visit you recently participated in, you had a test that measured scarring or "fibrosis" of your liver. The results of this test indicate that you may have increased scarring of your liver. This test is not perfect and I suggest that you follow up with your doctor to discuss a plan for repeating the test (or a similar test) to confirm the results. There are many conditions which can cause liver scarring. If you do have liver scarring, your doctor may suggest additional tests to see what might be causing it."

Sample letter to PCP:

"Dear Dr. XX

Your patient, XX, underwent transient elastography (FibroScan) of their liver. This test was done for research purposes only. The results of the test indicate

that your patient may have significant scarring or fibrosis of their liver. Specifically, the liver stiffness value was XX KPa/IQR. I am alerting you regarding this test result so that you can put this result into the clinical context for your patient. I would suggest repeating this test (or a similar test evaluating liver fibrosis) in the clinical setting to confirm the finding and determine if the Framingham Heart Study result was a false positive. If your patient does have significant liver fibrosis, you should considering a work up to determine the cause of the liver scarring and/or a referral to a hepatologist. Please do not hesitate to contact me if you have questions at 617-638-8392 or contact Maureen Valentino at 508-935-3417.

- Funding mechanism

This study is supported by the Boston University Department of Medicine, Division of Gastroenterology. Additional support for the study is from Echosens corporation and Gilead Sciences. The study has Third Party Review from the NHLBI.

Michelle T. Long
Framingham Heart Study Investigator
85 East Concord Street, 7th Floor
Boston, MA 02118
-Tel 617-638-8392 Fax 617-638-6529
mtlong@bu.edu

[DATE]

PCP Name
PCP Address

Dear Dr. XXX,

Your patient, _____, participated in the recent research examination at the Framingham Heart Study. In his/her consent form, your patient gave permission to provide findings of non-genetic research tests and examinations to him/her and to you as a physician or other health care provider. We are now providing you some findings as described below.

Your patient, XX, underwent transient elastography (FibroScan) of their liver. This test was done for research purposes only. The results of the test indicate that your patient may have significant scarring or fibrosis of their liver. Specifically, the liver stiffness value was XX KPa. I am alerting you regarding this test result so that you can put this result into the clinical context for your patient. I would suggest repeating this test (or a similar test evaluating liver fibrosis) in the clinical setting to confirm the finding and determine if the Framingham Heart Study result was a false positive. If your patient does have significant liver fibrosis, you should considering a work up to determine the cause of the liver scarring and/or a referral to a hepatologist. Please do not hesitate to contact me if you have questions at 617-638-8392.

We want to remind you that the research examination at the Heart Study is not clinical care and the testing is done for research purposes only. The research examination does not take place of medical care by a physician or health care provider and cannot be relied upon to identify health conditions. Research test measurements and findings are not the same as clinical test results. As such, our research examination is not necessarily performed by individuals with clinical training and qualifications, and many parts of the examination do not meet the standards for certified clinical testing. For these reasons, our research tests should not be relied on to make any diagnosis, treatment, or health planning decisions.

Warm regards,

Michelle T. Long, MD

Michelle T. Long
Framingham Heart Study Investigator
73 Mt. Wayte Avenue, Suite 2
Framingham, MA 01702-5827
-Tel 508-935-3417
mtlong@bu.edu

Participant Name
Participant Address

Dear XXX,

Thank you again for participating in the recent research examination at the Framingham Heart Study. In your consent form, you gave permission to provide findings of non-genetic research tests and examinations to you and/or your physician or other health care provider. We are now providing you and your health care provider some findings as described below.

At the Framingham Heart Study visit, you had a test that measured scarring or "fibrosis" of your liver. This test was done for research purposes only. The results of this test indicate that you may have increased scarring of your liver. This test is not perfect and I suggest that you follow up with your doctor to discuss a plan for repeating the test (or a similar test) to confirm the results. There are many conditions which can cause liver scarring. If you do have liver scarring, your doctor may suggest additional tests to see what might be causing it.

We want to remind you again that the research examination you had at the Heart Study is not clinical care and the testing is done for research purposes only. The research examination does not take place of medical care by your own physician or health care provider and cannot be relied upon to identify health conditions. Research test measurements and findings are not the same as clinical test results. As such, our research examination is not necessarily performed by individuals with clinical training and qualifications, and many parts of the examination do not meet the standards for certified clinical testing. For these reasons, our research tests should not be relied on to make any diagnosis, treatment, or health planning decisions.

Please contact Maureen Valentino if you have any questions at 508-935-3417.

Warm regards,

Michelle T. Long, MD

Diagram 1

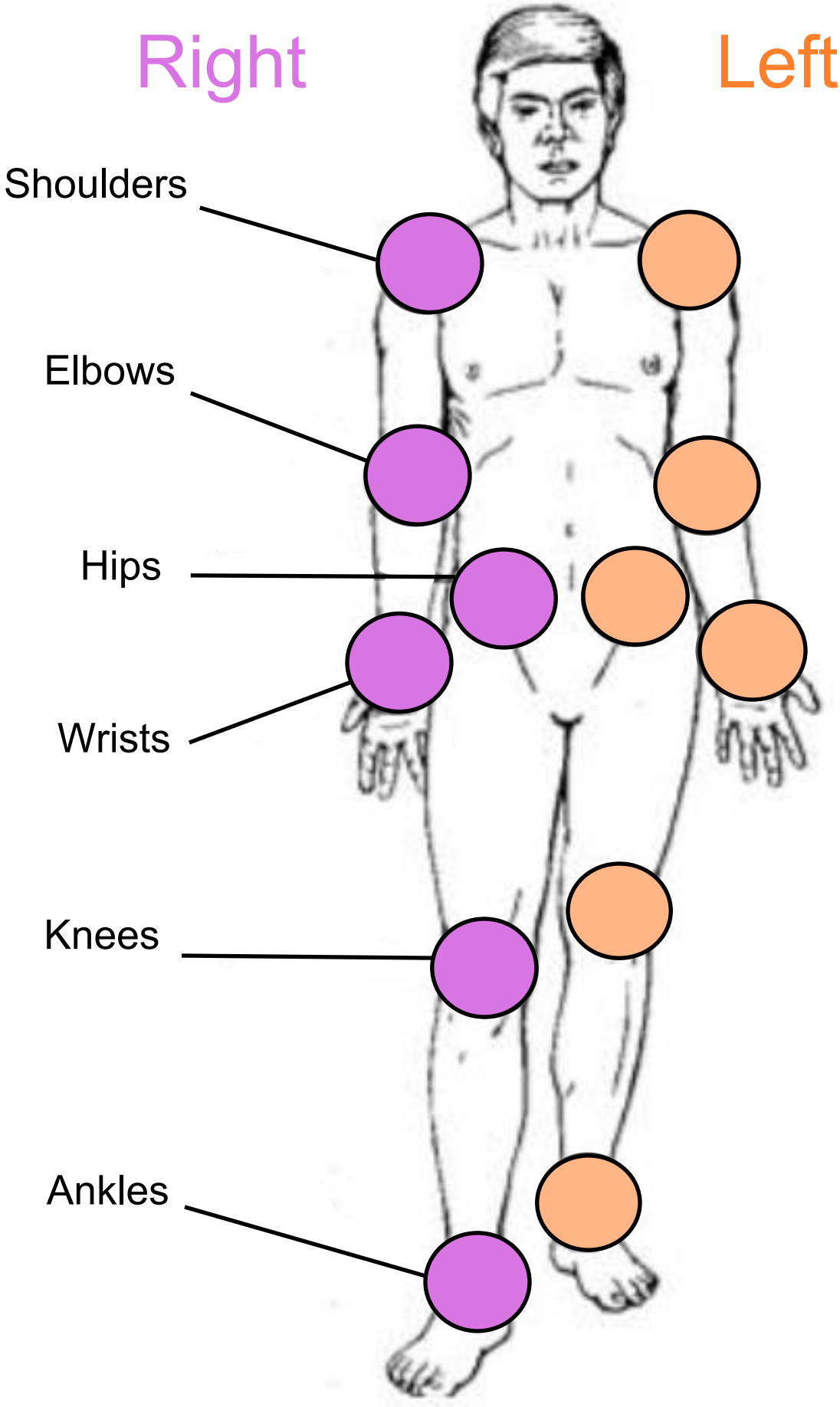
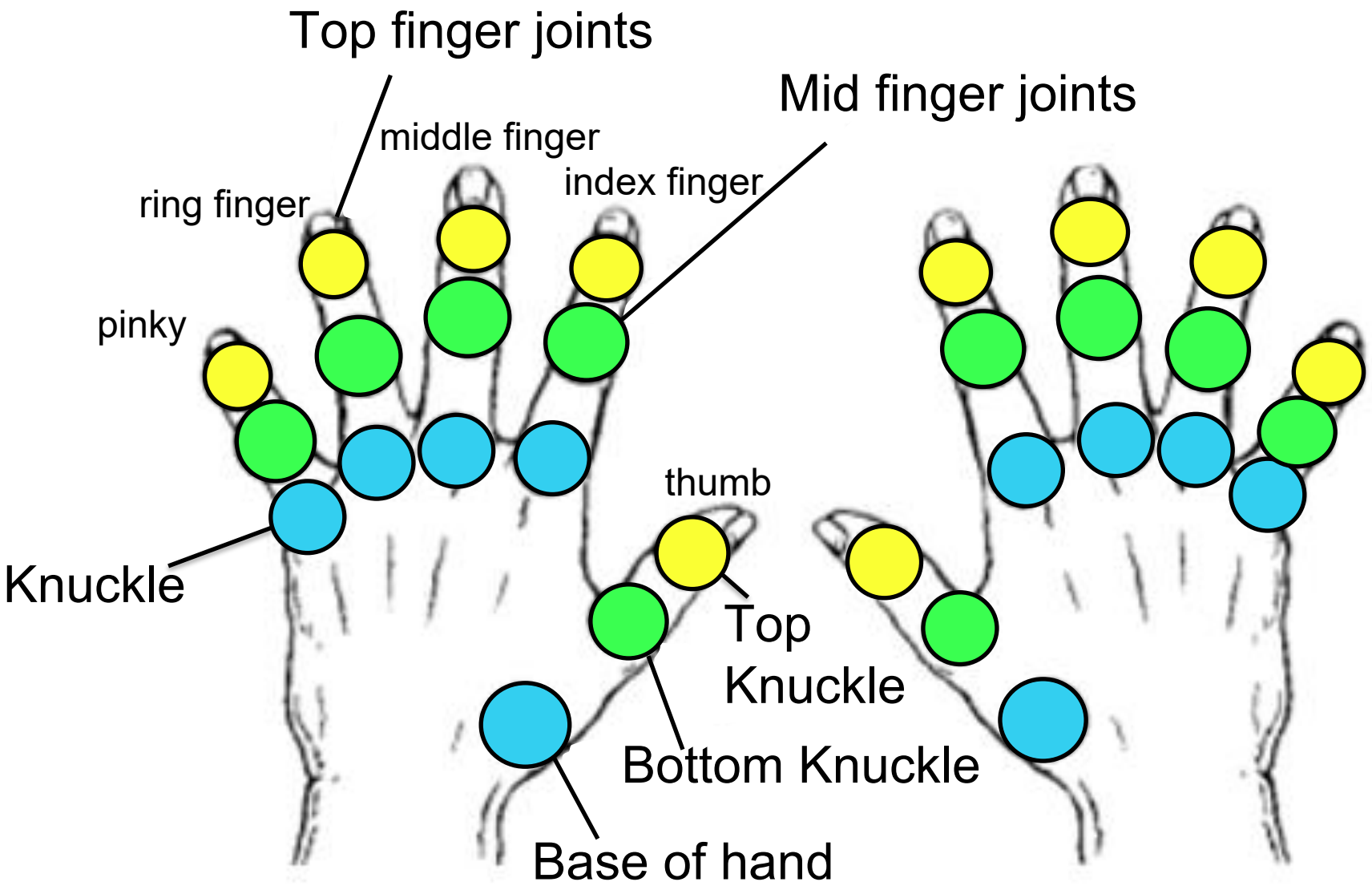
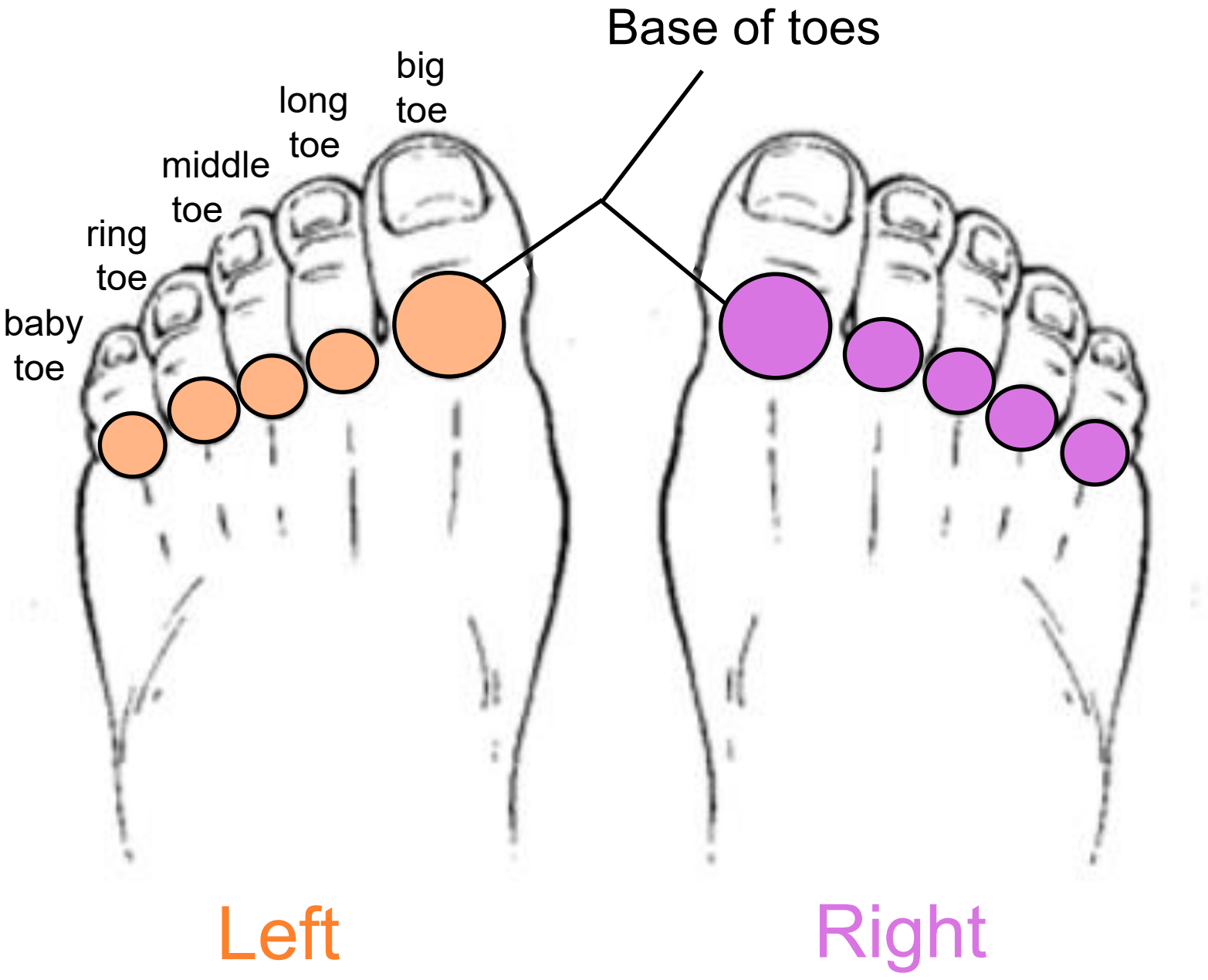


Diagram 2



Hands: Joints Palms Dowm

Diagram 3



Joints at Base of Toes

Diagram 4

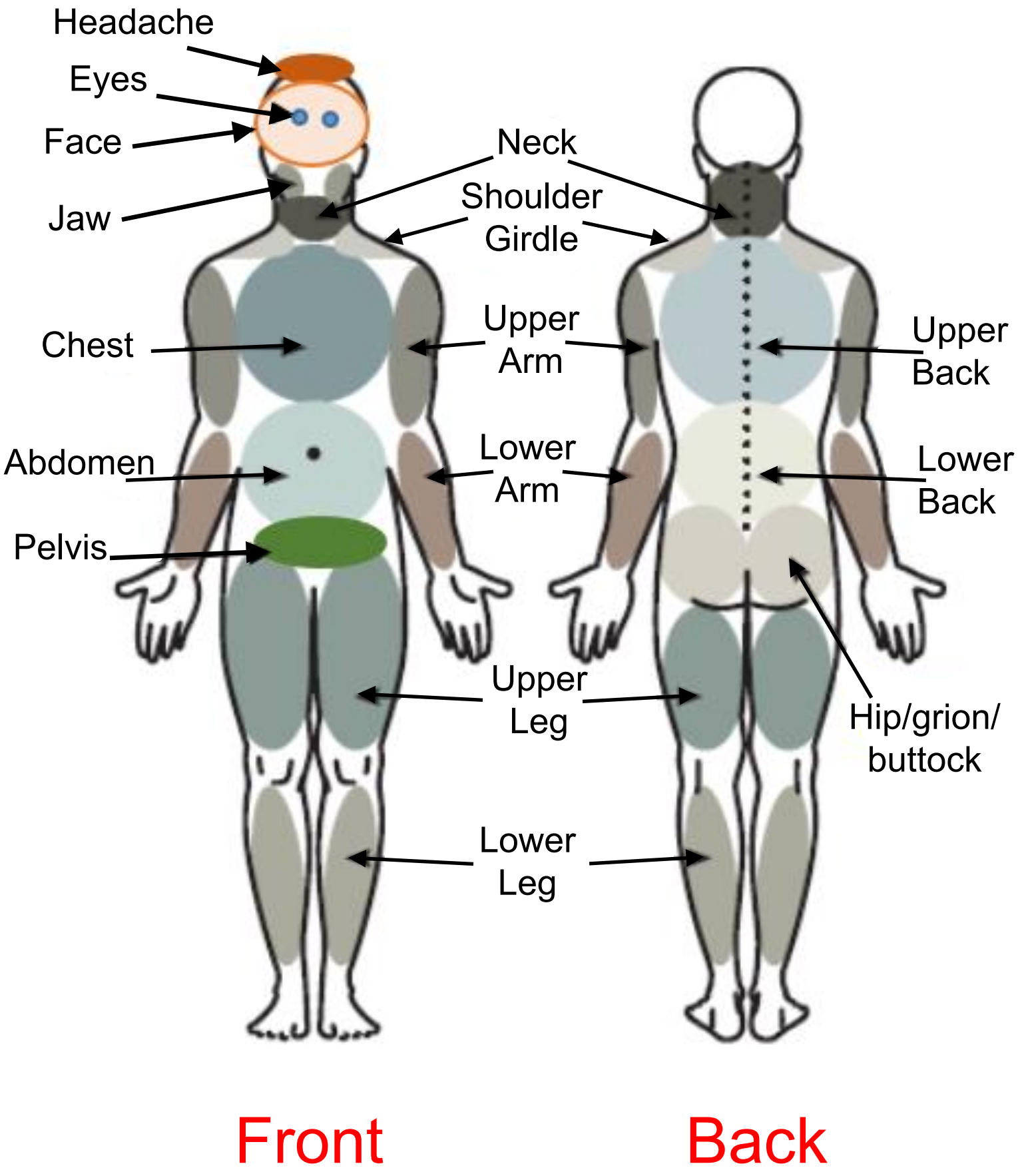
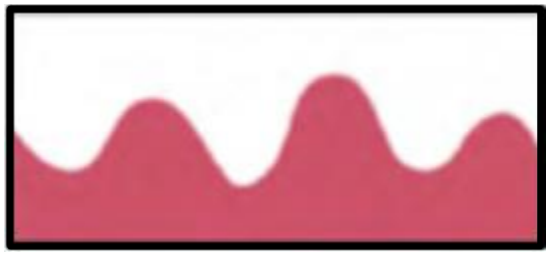

Headache
Eyes
Face
Jaw
Neck
Shoulder Girdle
Chest
Upper Arm
Upper Back
Abdomen
Lower Arm
Lower Back
Pelvis
Upper Leg
Hip/grion/ buttock
Lower Leg
Front
Back

Diagram 5

#1: Persistent pain with slight fluctuations

#2: Persistent pain with pain attacks

#3: Pain attacks without pain between them



#4: Pain attacks with pain between them

#5: No pain

FHS CAPSITE 2523

Pain Questionnaires & Quantitative Sensory Testing Operations Manual

Table of Contents

1. Background and rationale

In FHS CAPSITE, we are interested in understanding the pain experience of individuals, particularly that of older adults in the community. We will assess aspects of their pain experience by self-administered questionnaires. In addition, we will assess measures related to pain sensitization as an examination of its contributions to chronic pain in older adults in the community. We will assess pressure pain threshold (**PPT**) as a measure of ascending pain pathways, and conditioned pain modulation (**CPM**) as a measure of descending pain pathways.

2. Interviewer-assisted questionnaires (IAQ)

The first part of this assessment will be a series of questionnaires that will be administered by the interviewer, with responses recorded into RedCap by the interviewer. The interviewer should remain neutral, encouraging the participant to respond to the best of their ability. The Questionnaire can be found in Section **8** "**Data Collection Forms**".

Televisit: This assessment will be a series of questionnaires that will be administered by the interviewer via Zoom or by phone, with responses recorded into RedCap by the interviewer.

Script: "In this part of your study visit, we are interested in understanding what your experience of pain may be like. There are no right or wrong answers. We also understand that pain can change from day-to-day. Just answer to the best of your ability when thinking about any pain you may have had in the past week."

2.1 General Pain Questions

Questions #1-4: These questions ask about average pain, constant pain, and pain that comes and goes over the past week. For Question #1, use the laminated card #1 that shows the 0-10 pain scale ('no pain' to 'pain as bad as you can imagine'). For Question #3, use laminated card #2 that shows the 0-4 frequency scale (not at all/no pain, rarely, sometimes, often, very often).

Televisit: For Question #1 and Question #3 share screen via Zoom screen share. If video is not available, read out answer choices to participant.

2.2 Pain Interference from the Brief Pain Inventory

Question #5: If there was no pain in the past week, these questions are skipped. Question #6: These questions ask about how much pain has interfered with various aspects of life. Use laminated card #3 that shows 0-10 interference scale ('does not interfere' to 'completely interferes').

Televisit: For Question #6, share scale via Zoom screen scare, if video is not available read out answer choices to participant.

2.3 Three-item Pain Catastrophizing Scale

Question #6: These questions ask about thoughts/feelings about pain. Use laminated card #4 that shows 0-4 degree scale (not at all, to a slight degree, to a moderate degree, to a great degree, all of the time). If questions 1-5 are marked "no" or "no pain" for all questions, the interviewer can mark "not at all" to A, B, and C without asking the participant this question.

2.4 Joint Homunculus

Question #7: This will be skipped if there was no pain, aching, or stiffness in the joints on most days over the past week. If the response to the question is yes, then show **Diagrams #1-3 (Appendices A-C)** for body joint areas that the participant can indicate as having pain/aching/stiffness, which the interviewer should document in RedCap survey.

If a participants responds that the entire hand (left and/or right) hurts in Diagram 2, confirm that they mean every joint in the hand, and then select all knuckle joints, mid finger joints, and top finger joints for the thumb, index finger, middle finger, ring finger, and pinky. Then refer to Diagram 1 and ask "Does that include your wrist?". If yes, then refer to the previous question regarding body joints and select "wrist" for the appropriate side of the body.

If a participant responds that the entire foot hurts in Diagram 3, confirm that they mean every joint in the foot, and then record select all base of toe joints for big toe, second toe, 3rd toe, 4th toe, and 5th toe. Then refer to Diagram 1 and ask "Does that include your ankle?". If yes, then refer to the previous question regarding body joints and select "ankle" for the appropriate side of the body.

Televisit: Share these diagrams via Zoom screen. If video if not available, say "I am now going to ask you about which joints may have pain, aching, or stiffness during the past week." and then list the joints. Next say, "Anywhere in the left hand did you have pain, aching, or stiffness during the past week?" and list the finger joints in the left hand (knuckles at the top of the palm, middle joints, joints by the fingernails). Next say, "Anywhere in the right hand did you have pain, aching, or stiffness during the past week." and list the finger joints in the right hand. Now move onto the joints at the base of toes and say, "Now thinking about your left foot, did you have any pain, aching or stiffness in the joints at the base of your toes?" and list the toe joints. Lastly say, "Now thinking about your right foot, did you have any pain, aching or stiffness in the joints at the base of your toes?" and list he joints in the right foot.

See Diagrams 1-3

2.4 Widespread Pain Index

Question #8-10: This question asks about pain or tenderness in body regions ***other than the joints***. Show **Diagram #4 (Appendix D)** for the body regions the participant should consider. The interviewer will document all areas in RedCap Survey. If the participant repeats areas that were already mentioned in #7, ask them to clarify whether the pain they are commenting on in that region now is different from what they were referring to in the prior question.

Televisit: If video is not available say the following: "Next, please consider any pain or tenderness in body regions OTHER THAN YOUR JOINTS. Do you have pain or tenderness during the past week in different part of your body other than your joint?" and then list the body parts.
See Diagram 4

The next question (#9A-D) asks about severity of other symptoms the participant may be experiencing. Use laminated card #5 for the 0-3 problem scale (no problem, slight/mild problem,

moderate problem, severe problem).

Televisit: For Question #9 (A-D) share this scale (#5) via Zoom screen share, if video is not available read answer choices to participant.

Then the final question (#10) in this section asks about the most painful body site(s) based upon what was answered in #7 and #8. Participants can choose more than one body site (e.g., perhaps more than one site is equally painful). If only a single site was listed in #7/#8, only that site will be listed in #10; that site can be marked by the interviewer without asking the participant.

This question (#10) will be skipped if no body sites were marked as painful in #7 or #8. If multiple sites are marked but the participant is having difficulty selecting a single site, encourage the participant to select the most severe site, and if they cannot select a single one, they should select more than one (e.g., more than one may be equally severe).

2.5 PainDetect

Question #11: This series of questions asks about pain patterns and potential indicators of neuropathic-like pain. For the pain patterns, show **Diagram #5 (Appendix E)**. Then use laminated card #6 for the 0-6 strength scale (never, hardly noticed, slightly, moderately, strongly, very strongly) for the remaining questions. If no pain is reported on all prior questions, questions 11, 12, and 13 will not be asked of the participant. Instead, the interviewer will record responses to question 11 as “no pain”, question 12 as “no”, and question 13 as “never” to all sub questions.

Televisit: For Question #11 show diagram #5 via Zoom screen share, if video is not available skip question 11.

See Diagram 5

After completion of the questionnaires, prepare for the pressure pain threshold + conditioned pain modulation protocol.

Televisit: The pressure pain threshold + condition pain modulation protocol will not be performed in a televisit. **Interviewer should enter on T15 Form intentionally left blank and select “other”, in the “other -reason why form was left blank” enter “no-in-person visit”.**

3. Equipment and supplies

- Pressure Algometer (FDIX25 digital algometer)
- Blood pressure cuff
- Stress ball (with FHS CAPSITE logo)
- Stop watch (+/- metronome or metronome app on smart phone set to 60 beats per minute, with no time signature or 1/4 time)
- Pen or marker for anatomic location marking
- Chair without wheels

3.1 Service and maintenance

3.1.1 Pressure algometer

Contact information:
Wagner Instruments

Tel: 1-800-345-4188; 1-203-698-9681
sales@wagenerinstruments.com

Contact person: Bill Wagner

3.2 Calibration

3.2.1 Calibration of algometer against certified weights

The algometer should be calibrated monthly against a balance beam scale using certified weights of 10 and 25 pounds.

3.2.2 Examiner monthly algometer calibration

Examiners performing pain sensitivity testing must be tested on a monthly basis to insure that they are applying algometer pressure at a consistent rate of 5 kg at 10 seconds +/- 1 second and 7 kg at 14 seconds +/- 1 second. The Algometer Monthly Examiner Calibration Log (located xxx) must be completed each time examiner calibration is completed.

4. Safety issues and exclusions

4.1 Safety issues

Although rare, there is the potential for skin irritation and redness or bruising during testing. Bruising or discomfort could potentially result from application of the pressure algometer during pressure pain threshold testing and/or blood pressure cuff inflation.

4.2 Exclusions and determination of anatomic sites to use/test

Pressure Pain Threshold assessment at the Right Trapezius
Any recent injury or trauma to the trapezius (“top of the shoulder”) that would preclude application of any pressure.

Evaluation of exclusions for blood pressure measurement
Another factor in the determination of which wrist to use will be determined by which arm can have a blood pressure cuff inflated for conditioned pain modulation (CPM) assessment. Ideally, the left arm should be used for blood pressure cuff inflation to allow the right wrist to be used for this protocol. Please see detailed CPM exclusions in Section 4.1.6.

The arm-specific exclusions for blood pressure cuff inflation are:

- Lymphedema
- Takayasu’s arteritis

If the left arm meets any of these exclusions but the right arm does not have an exclusion, then the right arm must be used for blood pressure cuff inflation. ***This would mean that the LEFT trapezius should be used for PPT and CPM. This is because the arm used for blood pressure cuff inflation MUST be contralateral to the side being tested.***

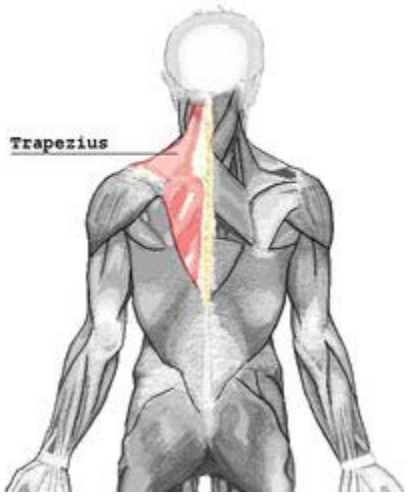
IMPORTANT NOTE: If the only arm that is eligible for blood pressure cuff inflation is ipsilateral to the only trapezius that can be tested, then only perform PPT testing, as CPM cannot be performed.

5. Participant preparation

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 cuff 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 the deltoid, with the algometer tip pointed downward at the mid-point between the neck and the edge of the shoulder (see photo and diagram). 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.



5.1 Detailed measurement procedures

5.1.1 Quantitative sensory testing

Quantitative sensory testing will be assessed in a standardized manner an algometer to assess pressure pain threshold (PPT) and conditioned pain modulation (CPM) at the trapezius. These measures should generally not be painful, although there may be some transient discomfort for some. They may, however, evoke painful responses in the presence of, for example, peripheral or

5.1.2 Order of testing

PPT
CPM

5.1.3 General instructions

Equipment (see Section 2)

- Pressure Algometer (FDIX25)
- Blood pressure cuff
- Stress ball
- Stop watch, metronome app (set to 60 beats per minute, 1/4 time or no timesignature)

At the beginning of each day, place each of the instruments to be used on a small tray table, in order of use (e.g., pressure algometer, blood pressure cuff). All items that touch the skin (algometer tip) must be cleaned with alcohol after use on each participant. The pressure algometer should only be turned on when ready for use. At the end of the day, plug in the algometer to recharge it. If the algometer reads low battery, the device may be used while plugged in.

Participant positioning
The participant should wear a shirt/gown/robe with a loose collar that allows the trapezius to be exposed. Have the participant sit comfortably in a chair without wheels with their arms resting in their lap. The participant will be asked to look straight ahead during each testing procedure after first having the demonstration of what the instrument looks like, what you will be doing with it.

The nature and the purpose of the tests should first be explained to the participant (see Script in Section 5.1.4).

5.1.4 Pressure pain threshold and conditioned pain modulation

Equipment (See Section 2)

- Pressure Algometer (FDIX25)
- Blood pressure cuff
- Stress ball
- Stopwatch

The pressure pain threshold (PPT) assessment will be performed at the ***right*** trapezius, unless exclusions require the LEFT side to be used. Before having started the QST protocol, the examiner should have already determined eligibility for including the conditioned pain modulation (CPM) protocol with the PPT measurement, 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.

Prior to assessing which trapezius and arm to use for PPT and CPM, explain the following to the participant

Script: "In this part of your study visit, we are going to assess your body responds to pressure on your skin. Before we get started, I need to ask you a few questions to determine which shoulder and arm we are going to assess today."

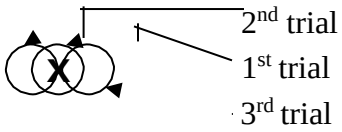
Exclusions for CPM

- MI within 6 months
- Severe peripheral vascular disease
- Any exclusions that were relevant for blood pressure measurement (See **4.2** and below)
    - Exclusions for *left* arm for 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 results in pulselessness/poor blood flow due to arterial narrowing)
        - Arteriovenous fistula for hemodialysis
    - There is no maximal BP exclusion; any maximal BP exclusion for the Core Contract would preclude the rest of the study exam.

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

The instrument looks like this:

For each site to be tested, center the rubber tip over the ‘x’ that is marking the site to be tested for the 1st trial. 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:



For each site being tested, try to ensure that the examiners arms are supported (e.g., both elbows tucked in at the examiner’s 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.

Script: “Everyone responds to discomfort in different ways. We are interested in how your body responds to pressure on your skin. There are no right or wrong answers. For this test, I’m going to place this device on the top of your shoulder. During this test, pressure will gradually be applied. We are interested in learning the amount of pressure at which you ***first*** begin to experience slight pain. As soon as the pressure from the test first produces slight pain, say ‘pain.’ We are not interested in how long you can tolerate the pain, but rather when the pressure first becomes slightly painful.”

Script: “Please tell me your understanding of what will occur during the test and what we’d like you to do.”

(Wait for participant’s response; reinforce the following script: “when pressure FIRST becomes slightly painful” as needed.)

Eyes remain open for this test.

Script: “Ok, I’m going to start at your right shoulder area.**”**

Apply the FDIX25 Algometer on the eligible trapezius (preferably right).

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.

(Tell participant before starting each trial so that they are primed to start concentrating as soon as the pressure begins e.g., script: “I’m starting the first/second/third test now.” After each test: script: “I’m just going to record that now.”)

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 9.99 kg is reached on the algometer without the participant reporting "now," terminate the trial and record as 10.00 kg.

Repeat this measurement three times.

Conditioned Pain Modulation (CPM)

Immediately upon completing the set of 3 PPTs at the trapezius, the CPM protocol will be initiated. Please note, prior to initiation of the Quantitative Sensory Testing protocol, it should have already been determined which arm is eligible for BP cuff inflation (preferably left arm).

Script: "We are now going to repeat the measurement to see if your pressure threshold changes in response to inflating a blood pressure cuff on your arm and squeezing a soft ball with your hand. After I inflate the cuff, I will ask you to squeeze the ball 10 times with your [left] hand at a rate of once per second. I will then ask you to rate any pain or discomfort you may have in your *forearm* on a scale of 0-10. I may ask you to repeat squeezing the soft ball until your level is ready for us to repeat the pressure threshold."

If the right trapezius had PPT assessed, then the left arm should be used for BP assessment. Elevate the index arm to chest level. Place the blood pressure cuff around the middle of the upper arm as for blood pressure measurement, with the lower edge of the cuff ~3cm proximal to the antecubital fossa. Inflate the cuff to 10 mmHg above the systolic blood pressure that was already recorded at the NP station (should be auto-populated into RedCAP). If it was not recorded, then inflate the cuff to 10mmHg above the loss of the radial pulse being palpable.

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

Script: "Please rate any pain or discomfort you may have in your forearm now on a 0-10 scale?"

- If pain is <4/10, ask subject to continue with another set of 10 hand exercises; repeat pain rating and hand exercise as needed until ii), iii), or iv) occurs.
- If pain ≥4/10, subject can discontinue hand exercises → go to PPT
- If pain is unbearable and subject requests cuff deflation → deflate cuff, go to PPT
- If cuff has been inflated for 2 minutes without pain ≥4/10 → 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) [3 trials, as per the initial assessment]. Unless the pain is unbearable and the subject 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.

Safety

- Stopping rules for cuff inflation, whichever occurs first:
  - Completion of PPT measurements;
  - Upon subject request;

6. Alert values, follow-up and reporting to participants

6.1 PPT and CPM

There are no 'right or wrong' answers. The PPT and CPM measures do not have clinical interpretations.

7. Quality assurance

7.1 Training and certification

"Master" examiners will train the clinic staff who will be administering the quantitative sensory tests. Clinic staff require no special qualifications or experience to perform this testing. Staff will be initially certified following the below certification requirements. The Pressure Pain Threshold exam will require a second 'master' certification by the 'master' examiner. Staff will be retrained and recertified midway through each examination cycle. Experience in musculoskeletal examinations is preferred but not required. Training should include:

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

7.2 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 completed QC checklist

7.3 Quality assurance checklist

General preparation for tests

- ☐ Participant wearing appropriate shirt
- ☐ Participant positioned properly on chair
- ☐ Anatomic landmark found and marked properly

Exclusions

- ☐ All exclusions correctly assessed and documented

Pressure pain threshold

- ☐ Correct script used to introduce test
- **Right** ☐ **Left** ☐ Algometer applied to trapezius until participant reports slight pain (x3)

Conditioned pain modulation

- ☐ Correct script used to introduce test
- ☐ Blood pressure cuff applied correctly
- ☐ Correctly proceeded to PPT after required pain rating or time limit
- ☐ Algometer applied to trapezius until participant reports slight pain (x3)
- ☐ Correct duration of cuff inflation

- ☐ Reviews form for completeness
- ☐ Correctly completes and submits form

8. Data collection forms

Please see the associated PDF documents on the following pages.

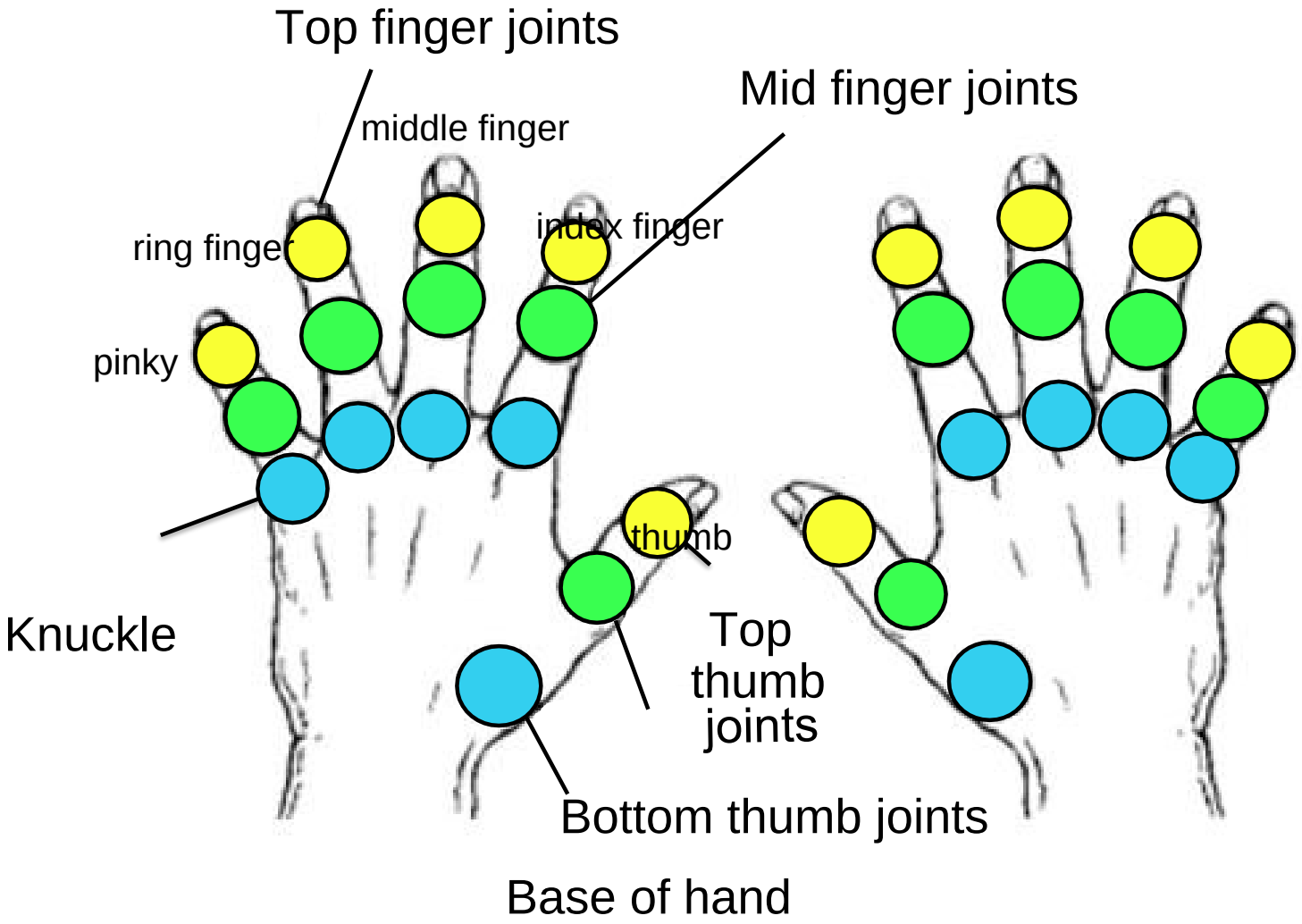
Appendix A: Community Assessment of Pain and Sensitization in the Elderly Data Collection Form

Please see annotated forms for this Questionnaire

Appendix B: Pain Pressure Threshold (PPT) and Conditioned Pain Modulation (CPM) Data Collection Form

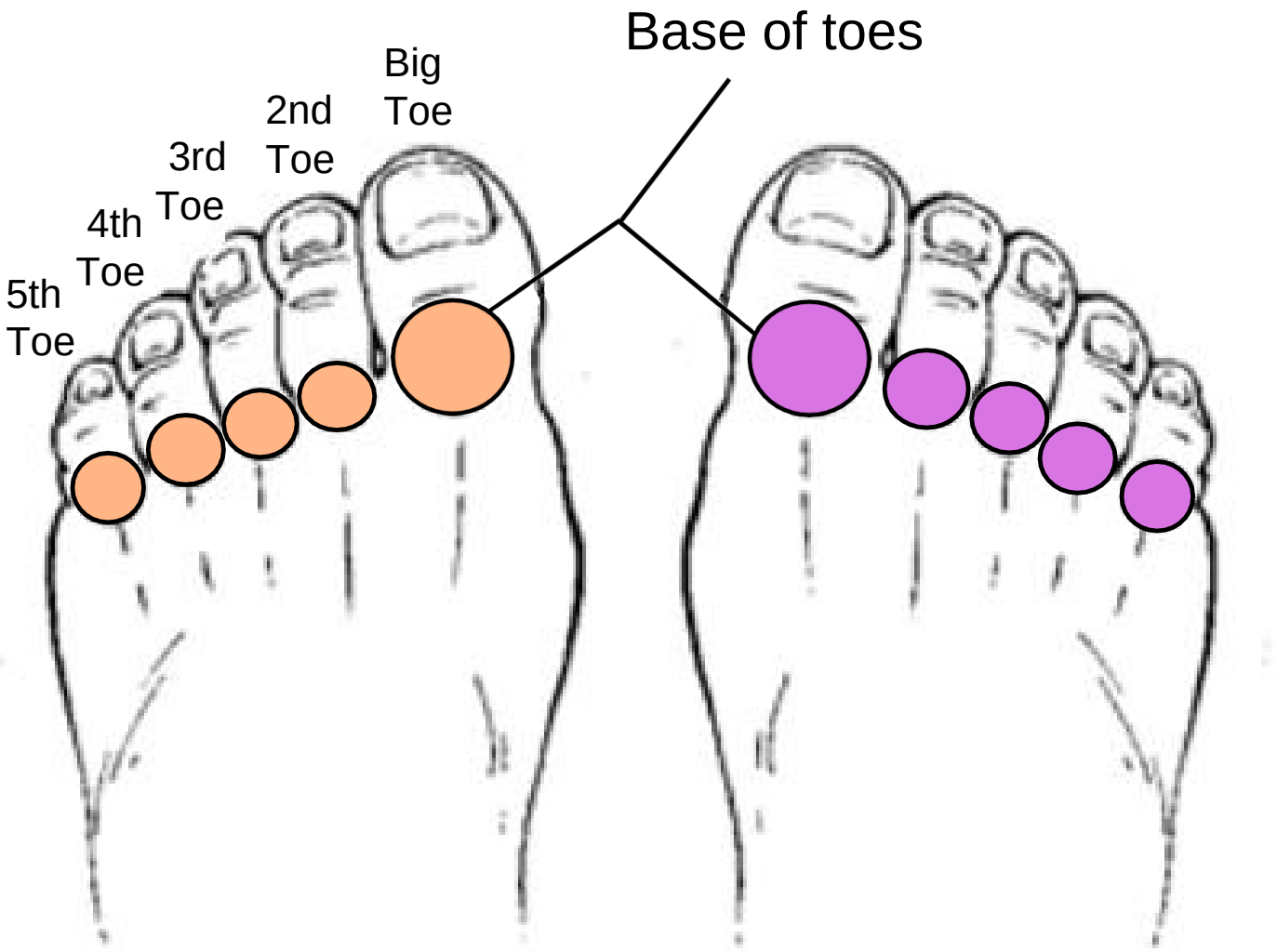
Please see annotated forms

Appendix D: Diagram 2 Hand Joint Palms Down



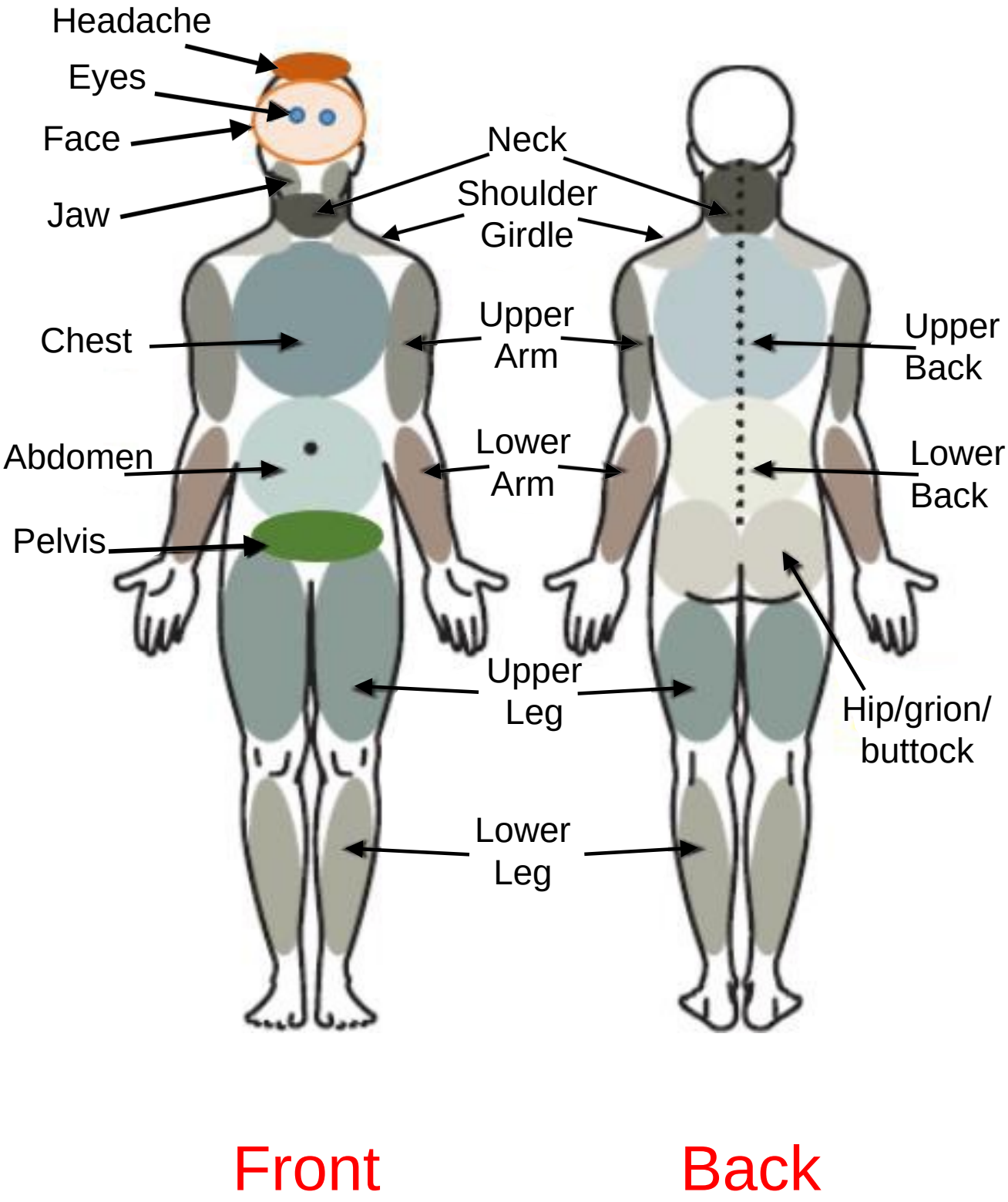
Hand Joint Palms Down

Appendix E: Diagram 2 Base of Toes Joints



Joints at Base of Toes

Appendix F: Diagram 4 Body Pain

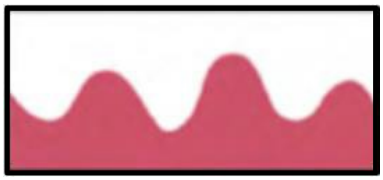


Appendix G: Diagram 5 Pain Experience

#1: Persistent pain with slight fluctuations

#2: Persistent pain with pain attacks

#3: Pain attacks without pain between them



#4: Pain attacks with pain between them

#5: No pain

Pressure Pain Threshold (PPT) and Conditioned Pain Modulation (CPM)

Screening:

Pressure Pain Threshold (PPT) will be applied to the RIGHT trapezius, unless contraindicated:

1. Has there been any recent (<6 weeks) trauma/injury to RIGHT trapezius?

○ Yes → Go to **#2**

○ No → Use **RIGHT** trapezius for PPT

2. Has there been any recent (<6 weeks) trauma/injury to LEFT trapezius?

○ Yes → **PPT cannot be performed; go to #5**

○ No → Use **LEFT** trapezius for PPT

The Conditioned Pain Modulation (CPM) protocol requires application of a blood pressure cuff to the arm opposite to the side that will have PPT assessed.

3. Are there any contraindications* to applying a blood pressure cuff on the LEFT arm?

○ Yes → Go to **#4**

○ No → Use **LEFT** arm for BP cuff inflation

4. Are there any contraindications* to applying a blood pressure cuff on the RIGHT arm?

○ Yes → Cannot perform CPM

○ No → 4a. Are there any contraindications to using the **LEFT** trapezius?

- ○ Yes → Cannot perform CPM
- ○ No → Use **LEFT** trapezius for PPT and **RIGHT** arm for BP

**Blood pressure contraindications: Heart attack within past year, documented history of Raynaud's syndrome or disease, severe peripheral vascular disease, lymphedema (for example, with mastectomy), Takayasu's arteritis, fistula in the arm, or any other blood pressure contraindications..*

5. Can PPT be performed?

○ Yes → Go to **#6**

○ No → **STOP: end of test**

6. Which trapezius will be used for PPT?

○ **Right arm** ○ **Left arm**

7. Can CPM be performed?

○ Yes → Go to **#8**

○ No → **Only perform PPT**

8. Which arm will be used for BP cuff inflation for CPM (*must be opposite to trapezius being tested for PPT)?

○ **Right arm** ○ **Left arm**

Data Collection:

PPT:

Trapezius (right preferred)	**Trial 1**	**Trial 2**	**Trial 3**□
○ **Right used** ○ **Left used**	□□.□□ **kg** ○ Test Not Done	□□.□□ **kg** ○ Test Not Done	□□.□□ **kg** ○ Test Not Done

CPM: 2nd PPT (Post-BP Cuff inflation PPT)

"We are now going to repeat the measurement at the same spot on your trapezius to see if your exam changes in response to inflating a blood pressure cuff on your arm and squeezing a soft ball with your hand. After I inflate the cuff, I will ask you to squeeze the ball 10 times at a rate of once per second. I will then ask you to rate any pain you may have in your forearm on a scale of 0-10. I may ask you to repeat squeezing the soft ball until your level is ready for us to repeat the exam."

Systolic blood pressure (Refer to BP measurement): ☐☐☐ **mm Hg**

Examiner note: *Inflate BP cuff to ~10mm Hg above systolic level and record inflation time:*

☐☐ **Minutes** ☐☐ **Seconds**

Number of hand squeezes (grips) done: ☐☐

Examiner note: *If pain rating is less than 4 after 10 ball squeezes, ask participant to squeeze ball in increments of 10 more times, asking for a pain rating each time. If 2 minutes has passed with pain rating ≥4/10, go to second set of PPT*

"Please rate any pain you may have in your forearm now on a 0-10 scale, 0 being no pain."

Final Pain Rating prior to performing 2nd PPT:

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10

Examiner note:

- If cuff is inflated for 2 minutes without pain rating of 4 or more, perform the PPT assessment. Mark the final pain rating prior to the PPT assessment and record the inflation time.
- Hand squeezes (grips) are discontinued whenever the participant reports pain of 4 or more. At that point, perform the PPT assessment. Mark the final pain rating prior to the PPT assessment and record the inflation time.
- At any time, discontinue cuff inflation at participant's request if pain is unbearable. The PPT assessment can be performed with the cuff deflated if the participant does not object to completion of the exam. Mark the final pain rating prior to the PPT assessment, and record the inflation time.
- Deflate cuff after 3rd PPT measurement is obtained.

2nd PPT:

Trapezius (right preferred)	**Trial 1**	**Trial 2**	**Trial 3**□
○ **Right used** ○ **Left used**	☐.☐☐ **kg** ○ Test Not Done	☐.☐☐ **kg** ○ Test Not Done	☐.☐☐ **kg** ○ Test Not Done

Was the cuff deflated prior to completion of the PPT assessment?

○ Yes ○ No

Equipment Calibration – Summary

Algometer	**Monthly:** Task 1: Use calibrated scale. Scale weight is set to 10 pounds and Examiner 1 presses down on scale with rubber pad of algometer, keeping the device vertical and with peak hold on. Examiner 2 watches balance beam and lets Examiner 1 know when balance is achieved. The reading on the algometer should fall with +/- .5 pound for 10 pounds. Task 2: Use calibrated scale. Scale weight is set to 25 pounds and Examiner 1 presses down on scale with rubber pad of algometer, keeping the device vertical and with peak hold on. Examiner 2 watches balance beam and lets Examiner 1 know when balance is achieved. The reading on the algometer should fall with +/- 1 pound.
Blood Pressure	**<u>Automated Oscillometric Device</u>** **With Each Use:** Task: Check that the connection of the cuff to the tubing is secure and tubing is not kinked. **Monthly:** Task 1: Inspect cuff and tubing for cracks or tears. Task 2: Check that all blood pressure cuff sizes are available. **Twice a year:** Inspect the tape used to measure arm circumference for damage or wear twice a year. **<u>Conventional Manometer</u>** **With Each Use** Task: Make sure needle is in the zero box. **Monthly:** Task 1: Check that needle rises smoothly and doesn't bounce when valve is closed. Task 2: Check cuffs, pressure bulb, and manometer for cracks or tears. Task 3: Check pressure control valve for sticks or leaks. Task 4: Check stethoscope tubing and diaphragm for cracks or tears. Task 5: Check blood pressure cuffs for air leaks. **Twice a year:** Inspect the tape used to measure arm circumference for damage or wear twice a year.

FHS Gen2/Omni1 Exam 10/5 Platelet Study

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Background notes: Very similar protocols were proposed and run in the last Framingham Heart Study exam. Thus, we are experienced with running these assays and instruments, their quality control and analysis.

Total burden to all protocols listed here:
1) Bleeding history questionnaire (<=5 min, self-administered)
2) 3x4.5mL sodium citrate blood tubes (Roche); 2x1.6mL hirudin blood tube (Sarstedt)

Staff training: Several members of our staff have years of experience with these instruments and protocols. Any new staff will be trained by experienced staff through shadowing, and use of these detailed written protocols. Periodic volunteer QC blood draws may also be used, particularly in the time period before the actual exam starts. There are no clinically reported results from these protocols so certification is not required.

Equipment and calibration schedule
(note in this setting all instruments are RUO):

1) Bio/Data PAP-8E light transmission aggregometer
   daily QC checks built-in; yearly LTA-Check test run and certified
2) Multiplate (Roche) impedance aggregometer
   daily QC checks built-in; monthly Liquid controls are run
3) T-TAS instrument
   there is routine maintenance/changing pump oil, etc but no specific calibration; there are built in pump and camera sensors that will trigger errors if there are major issues
4) Optimul absorbance assay/plate reader/freeze drier
   no specific maintenance; QC as below
5) microVISC viscometer
   the microVISC has built-in sensors if flow or other technical issues are experienced; QC as below
6) BD Biosciences Accuri C6 flow cytometer

under service contract; but no specific calibration; instrument has daily setup and shutdown checks and cleaning (which will trigger errors if there are major problems)

7) Centrifuge, heat block, plate washer and other basic equipment
   no specific maintenance schedule but all equipment new within the last several years; plate washer will detect if things are out of alignment

Quality control and certifications:

No specific certifications are required as we are not reporting clinical results. The PAP-8E does get re-certified annually.

We conduct detailed QC analyses as we have done in the last exam. This includes examination of month-to-month and/or batch-to-batch variation; and utilization of blinded, phantom blood-draw tubes periodically (about 3.5% of samples) to assess assay reproducibility and whether there are any systematic changes that would require troubleshooting.

Data collection:

1) We keep a paper log of lab processing – for example time of blood draw, time of each assay step, time of centrifuge, volume of PRP, and any other notes on particular samples or assays. These paper logs are entered into a computer log to help with potential analysis and trouble-shooting later if needed
2) RedCap – bleeding history questionnaire
3) Instrument data

Medically actionable results: as with the last exam these assays are RUO and there is no likely reportable finding.

Detailed Exam Procedures:

1) Bleeding history questionnaire (attached separately). Uses skip-logic. In our past experience, ~82% of participants answer No to all questions and will navigate quickly through the questionnaire without ever seeing an expanded question.
2) Lab preparation and measurement protocols. Detailed procedures follow for all steps on the following pages:
   a. Plasma preparation (p.3)
   b. PAP-8E LTA (p.4-9)

c. Multiplate (p.9-10)
d. T-TAS (p.10-17)
e. Viscometry (plasma/wb) (P.17-21)
f. Flow cytometry (P.21-23)
g. Making Optimul plates (P.23-28)
h. Optimul plate assay (P.29-30)
i. Preservation of samples for later use (P.30)

Plasma Preparation

Machine footprint (centrifuge): 24" (D) x 17"(W) x 14"(H)

Time (all samples): ~1 hour (most of this is not hands on time freeing personnel to work on other things; much of the extra time is due to spinning with no brake)

Timing is also dependent on sequence and clustering of blood draws. If blood draws are spread out over several hours, it is often best to have 2 rounds of spinning for PRP and PPP (early and later samples) so that assays can begin on the early samples

1.) Check and record the blood draw time in the data log.
2.) There should be 3 sodium citrate tubes (blue caps) for a normal draw.
    a. If there are fewer tubes, make a note in the data log.
    b. If there are 5 tubes, this means we have a "Phantom" for QC purposes. Record the phantom number in the phantom log.
3.) Let the plasma sit, undisturbed, on the benchtop for 15 minutes.
4.) Load the tubes in the centrifuge and spin on Program one to isolate platelet rich plasma (PRP)
    a. 10 min at 200 RCF.
    b. Acceleration setting is 3 and deceleration setting is 5.
5.) Pipette the PRP fraction of each sample into a 15mL conical tube.
6.) Recap the draw tube and return to the centrifuge.
7.) Spin tubes on Program 2 to isolate platelet poor plasma (PPP).

a. 15 min at 1,500 RCF.
b. Acceleration setting is 3 and deceleration setting is 5 (same as before)

8.) Remove the tubes from the centrifuge. You may now begin plasma testing.

PAP-8e LTA Operation

Machine footprint: 22"L x 14" W x 5" H

Time (per sample): ~15 minutes

Time (startup/walk away/shutdown/cleaning): 20 minutes for startup, agonist preparation,

releasates storage of all samples at end of day

Preparation:

1. Open the LTA software and click "Continue" to start the test block heating.
2. Pull out the test platform.
3. Remove pre-made agonists from storage and allow to warm to room temp.
    a. Collagen and Epinephrine are stored at 4C
    b. Ristocetin, TRAP-6 amide, and Arachidonic Acid are stored at -20C
4. Prepare fresh 9.5µM, 18.2 µM, and 57.1 µM ADP solutions.
5. Once the machine has reached 37C, log in and proceed to sample testing.

Sample Testing:

Note: this monitor is a touch screen. You may use touch or the mouse at any point, according to your preference. Moisture in the touch screen may cause difficulties and should be wiped immediately.

1. Click "Routine Aggregation."
2. A menu will pop up. Select "Multiple Tests" from the dropdown menu and click ok.

3. On the next screen, click “Run Sample.”
4. On the next screen, scan the appropriate sample ID into the first two fields in ROW 1.
5. Click “Fill Down,” then click in the second field in ROW 8. All of the first and second fields should auto-populate with the sample ID scanned into ROW 1.
6. Click “Template.” A new screen will appear. In the dropdown menu, select the appropriate test template (ours is “fhsNEW”), then click “Load.” You will be returned to the previous screen.
7. The third column should have auto-populated with the following tests:
    a. Channel 1 – Arachidonic Acid (AA)
    b. Channel 2 – Collagen (Coll)
    c. Channel 3 – 9.5µM ADP
    d. Channel 4 – 18.2µM ADP
    e. Channel 5 – 57.1µM ADP
    f. Channel 6 – Epinephrine (Epi)
    g. Channel 7 – AggRecetin (Risto)
    h. Channel 8 – TRAP-6
8. Place a cuvette in each of the 8 slots at the back of the test platform, and one cuvette in one of the stirred incubation wells (for the blank). Make sure each cuvette is free of debris and scratches.
9. Place a magnetic stir bar in each cuvette, including the blank.
10. Pipette 25µL Normal Saline into the blank tube.
11. Check that the PPP and PRP tubes you are going to use match the sample ID on the screen.
12. Pipette 225µL of PPP into the blank tube.
13. Make sure the PRP tube is securely capped, and invert once (gently) to mix.
14. Pipette 225µL of PRP into each of the 8 test cuvettes.
15. Click next. You will be brought to the test screen.
16. Move the blank into Channel 1, checking for stir bar and correct volume. Press cuvette down all the way.

17. Move the 8 test cuvettes to the stirred incubation wells (middle row on the test platform). Check for stir bar and correct volume in each cuvette.
18. Start the incubation timer by clicking any of the buttons at the top of the screen that display "0:00." This will begin a 2-minute countdown.
19. Close the channel covers, and click "Blank" for Channel 1. The button will gray-out and may blink for 1-10 seconds. This is normal.
20. When the letters turn black and the word "Start" replaces "Blank," you may open the channel cover. Opening the cover before blanking is complete may result in inaccurate blanking.
21. Move the blank cuvette to Channel 2 and repeat blanking procedure. Continue until all channels have been blanked.
22. When blanking is complete, move the test cuvettes forward into the test channels. Double check for stir bar and correct volume in each cuvette.
23. Firmly but gently, press down on each cuvette to ensure proper alignment. Mis-seated cuvettes will result in inaccurate data.
24. Close the channel covers.
25. When the timer beeps, begin agonist injection.
26. Pipette 25µL of the appropriate agonist (agonist order in Step 7) into each well. To proceed:
    a. Aspirate 25µL of agonist.
    b. Press "Start" on the computer screen for the desired agonist test channel. The button below will turn green and read "Inject."
    c. Set pipette tip in the correct slot, making sure the ridge of the pipette tip is flush with the cover surface, and dispense agonist.
    d. Press "Inject" on the computer screen.
    e. Discard tip, and repeat this step until all 8 agonists have been injected.
27. Click the "Test Block" tab (top right) to view data graph.
28. The test takes 6 min. from the "Start" time for each agonist. The timer will beep when each channel finishes.
29. When each test finishes, check the "Test Block" tab and review the aggregation plots.
    a. Click the "Status" button

b. If sample passes, click "Accept."
c. If sample fails, click "Reject." Record reason for rejection in the Data Log. Common reasons for rejection include:
    i. Incorrect or suspected incorrect agonist injected.
    ii. Cuvette was not pressed down.
    iii. No stir bar.
    iv. Unusual sample profile. Repeat to confirm.
d. To enter a comment for any sample (optional) to so click "CMMNT" and enter it.
e. When you are done, click "Done."

30. Discard used cuvettes in the biohazard waste.
31. Click "Menu," and exit to the Main screen
32. Proceed to next Participant Sample and repeat Sample Testing procedure until complete.

LTA -saving sample releasates

Part 1: making the diclofenac-heparin solution

Heparin is a biologically active species. Different lots of lyophilized heparin may have different activity even if the weight is the same (e.i. 10mg of lot A might not be as active as 10mg of lot B). As such, calculations are done based on heparin activity rather than weight. The "U/mL" unit designates activity.

Heparin is sold both by weight as lyophilized powder or in solution at a designated activity. Either is acceptable for this assay. The Framingham Heart Study currently uses heparin from lyophilized powder

1.) Make a 500 U/mL heparin stock solution.
    a. If using heparin purchased in solution, dilute to correct concentration in DI water.
    b. If using heparin in powder form, do the following:

i. Determine the activity for the lot. If this information is not included in the product packaging, it can usually be found on the manufacturer's website by going to the product page and downloading the Certificate of Analysis for the desired lot. The lot's activity should be listed there (sometimes it is labelled "anti-xa"). The unit should be "U/mg" unless otherwise stated.

ii. Calculate the volume of water necessary to reach the desired concentration as follows:

[(Activity in U/mg) x (weight of vial in mg)] ÷ 500U/mL = X

where X is the volume (mL) of DI water used to resuspend the powder.

iii. Resuspend in appropriate amount of water.

c. Store solution at 4°C.

2.) Make the 1 mM Diclofenac Sodium + 10U/mL Heparin solution. The following recipe is enough for about 90 samples.

a. To a 50mL conical tube, add 95.4mg diclofenac sodium salt.
b. Add 3mL DMSO.
c. Vortex vigorously until the diclofenac is completely dissolved.
d. Add 24.6mL PBS.
    i. Do not add PBS until the diclofenac is completely dissolved, otherwise it will fall out of solution over time.
e. Add 600µL of 500 U/mL Heparin stock.
f. Invert to mix.
g. Store solution at 4°C. Solution is stable for at least one month.

Part 2: Saving the releasate

1.) Run PAP-8e LTA test (see LTA protocol above)
2.) Immediately upon test completion, add 25µL of the 1 mM Diclofenac Sodium + 10U/mL Heparin solution to each test cuvette, including the PPP blank.
3.) Use a transfer pipette to move the plasma from each cuvette to a separate well in a covered 96-well plate (must be rated to withstand a 10min spin at 1,000xg).

4.) Once all the LTA tests for the day are completed and plasma is removed to the covered 96-well plate, place plate in the centrifuge and spin for 10 minutes at 1,000xg to pellet platelets.
5.) Transfer the supernatant to a fresh covered 96-well plate, taking care not to carry over the pellet (pellet should be fairly tight and difficult to disrupt). This step is best accomplished with a p300 multichannel pipette.
6.) Seal the plate with a foil 96-well plate sealing sticker. Be sure to press seal firmly between wells to prevent spillover.
7.) Store the plate at -80°C until use.

Multiplate Operation

Preparation:

1. Turn on the heat block by opening the Multiplate software.
2. Fill the Normal Saline tubes and place them in the incubation slots to warm them.
3. Remove pre-made agonists from storage and allow to warm to room temp. (Collagen stored at 4C; Risto, TRAP, and ASPI are stored at -20C)
4. Prepare fresh 98.8µM ADP.
5. Once the Multiplate machine has been at 37C for 20 minutes, run the daily electronic QC.

Sample Testing:

1. Let the Hirudin blood sit, undisturbed, for at least 30 minutes post draw time.
2. Click "Auto Pipette." Scan the bar code for the first sample into the sample id field, and click "Use ID for all tests"
3. Select a test for each channel. They should be in the following order:
    a. Channel 1 – 1_ADP
    b. Channel 2 – 2_Collagen
    c. Channel 3 – 3_Risto
    d. Channel 4 – 4_TRAP
    e. Channel 5 – 5_ASPI
4. Place a test cell in each channel, making sure that the stir bar is in the bottom of each cell.
5. Connect each sensor cable to the corresponding test cell.
6. Click Start, check that the tests are in the correct order, and then click start again.

7. Pipette 300µM normal saline into each cell, following screen instructions. The machine is programmed to dispense the correct volume of fluid at each step.
8. Invert the Hirudin whole blood tube 6 times (gently).
9. Double check that the ID on the tube matches the ID on the screen.
10. Pipette 300µM whole blood into each cell, following screen instructions.
11. Wait for the incubation period (3 min).
12. When the machine dings, add the appropriate agonist to each test cell.
    a. Channel 1 – 20µL of 98.8 µM ADP
    b. Channel 2 – 20 µL Collagen
    c. Channel 3 – 50µL Risto
    d. Channel 4 – 20µLTRAP
    e. Channel 5 – 20µL ASPI
13. Wait until the test is done (6 minutes). Check that the CC is >0.985 and the DIFF is >20. If these criteria are not met, it may be necessary to re-run the test.
14. Once complete, click "Stop Channel," select "stopped channels," and click "OK."
15. Detach the sensor cables from the test cells, then discard the used test cells in biohazard waste.
16. Proceed to next sample and repeat Sample Testing procedure until complete.

T-TAS Protocol

Machine Startup

1. Turn on the T-TAS laptop.
2. Turn on the T-TAS machine (flip power switch on the right side).
3. Wait for the machine to turn on; it will make a few mechanical noises.
4. Open the T-TAS application.
5. A small window will open titled "Select Mode." Select "AR Standard/ PL Standard" and click OK.
6. Another small window will open titled "Select USB." Select "A7OOF9ES" (should be the only option), and click OK.
7. The application will open. At the bottom of the left-hand application window, there will be a yellow box that says "Under initializing," and a small window will open saying "WARNING! Don't touch PC & device for completion of device behavior."
    a. Wait for yellow box to turn grey and acquire the heading "Measure Result Status" before proceeding, then click OK in "WARNING!" window.

8. At the top of the application window, there is a “Chip Type” dropdown menu. Select “PL chip,” then click “DECISION.”
9. From the “Shear Selection” dropdown menu, select “Mid Shear (manual rec.)”
10. Check the oil tank volume.
    a. If the oil volume is greater than 1,700ul proceed to step 11
    b. If the oil volume is less than 1,700ul, fill the tank before proceeding. To fill:
        i. Check the tubing from the mineral oil bottle to the oil tank for bubbles. If there are bubbles:
            1. Click on the “System Check & Maintenance” tab.
            2. Towards the bottom, there will be a box labelled “Select Valve.” Select the “Tank” radial button.
            3. In the “Micro Pump” box, click “Injection.” The button will gray-out.
            4. The bubbles should now move through the tubing back into the mineral oil bottle. Once all of the bubbles have been removed from the line, click the grayed-out “Injection” button to stop the oil flow.
            5. Return to the “Measure” tab, and click the “Oil Supply” button.
            6. A window will pop up asking you to confirm starting the oil supply process. Click ok.
            7. The window will now read “Now Supplying Oil!” You may click “Stop” at any time to halt the process.
            8. The filling process will automatically stop when the tank is full, and a window will appear saying “Then, prior to use, ‘system check’ it.” Click OK.
            9. Proceed to step 11.
11. Click on the “System Check & Maintenance” tab.
12. Towards the bottom, there will be a box labelled “Select Valve.” Select the “Chip” radial button.
13. In the “Micro Pump” box, click “Injection.” The button will gray-out.

14. The if there are any bubbles tank-to-chip line, they should now move through the tubing and out the nozzle.
    a. Make sure to hold the nozzle away from the machine with a Kimwipe underneath to avoid dripping oil into the machine.
    b. There will almost always be bubbles in this line at the start of the day.
15. Once all of the bubbles have been removed from the line, click the grayed-out "Injection" button to stop the oil flow.
16. Wipe any excess oil off the nozzle and insert it firmly into the white SC fitting **without** removing the fitting from its resting place.
    a. You should hold the nozzle as vertical as you can when inserting it into the fitting to avoid warping the nozzle, which could impact data quality.
17. In the "System Check" box, click start.
18. A window will appear reminding you to insert the nozzle into the SC fitting if you have not already done so. Click OK to start the check. Do not touch the nozzle or adjust any settings while the check is running.
19. The check will automatically stop once completed, and the "Result" field will display the result.
    a. If "Result: Success," proceed to step 20.
    b. If "Result: Failure," remove the nozzle from the SC fitting and check the following:
        i. Re-examine the tank-to-chip line for bubbles (most likely issue).
            1. If found, repeat bubble purge (steps 13-16)
        ii. Check the oil tank for bubbles.
            1. If found, pump a small amount of oil back into the mineral oil bottle and re-fill the tank (step 10.b.i.).
                a. This may not remove bubble, but it should move it to a neutral position.
        iii. Examine the nozzle and SC fitting for debris.
            1. If found, gently remove debris with a Kimwipe.
        iv. Check for any leaks or bad connections in the oil line.
        v. Rerun the system check until "Result: Success."

20. Once the System Check passes, remove the nozzle from the SC fitting (you may remove the fitting from its holder to do this). Return the nozzle to its holder.
21. The T-TAS machine is now ready for sample testing.

Running a sample: PL-Chip

1. Remove appropriate number of test chips from the freezer and allow them to come to temperature (about 30 minutes, 2 tests per chip).
2. When you are ready to begin, remove the chip from the package, and set the chip on the warming block. The chip should remain there for no more than ten minutes.
3. In the "System Check and Maintenance" tab, make sure that the radial button in the "Select Valve" box is set to "Chip"
4. Click on the "Measure" tab.
5. Make sure chip type is set to PL-chip and shear is set to "Mid shear (Manual rec)".
6. At the top of the screen in the "Sample Name" field, enter the test name, making sure to include the participant ID number and the operator initials.
7. Move the camera arm up by squeezing the two metal plates together and sliding the camera arm up.
8. Remove the focus chip and set it aside (skip this step if not the first test of the day).
9. Remove the plastic stickers from the channels of the PL-chip, and place the chip lengthwise, lining up the indentations on the bottom of the chip with the corresponding protrusions on the machine surface.
10. Press the chip down so that it sits firmly on the machine surface, without wiggling.
11. Lower the camera arm so that it rests on the surface of the chip.
12. At the bottom of the screen in the "Camera" box, set the camera to the chip channel you will be using by clicking "move to (left or right) path." There will be a whirring sound from the machine as the camera moves, and you will see the repositioning in the camera window on the screen.
13. Adjust the camera position to capture desired portion of the chip.
    a. Adjust left/right position by using the knob closest to the power switch on the right side if the machine.

b. Adjust up/down position by using the up/down arrow buttons on the front of the machine.

14. Adjust the focus using the knob closest to the front on the right side if the machine.
15. Check the tank -to-chip line for bubbles. If present, remove by running oil though the line.
    a. Bubbles anywhere in the oil line or test assembly impact the pressure distribution in the test system and invalidate test results. It is imperative that there be no air bubbles anywhere in the assembly for collection of accurate and valid data.
16. Remove the nozzle from its resting place and hold it away from the machine.
17. Hold a Kimwipe below the nozzle to prevent oil spillage into the machine, and press the "OIL" button on the front of the T-TAS unit.
18. Once a small droplet of oil has emerged, wipe off excess oil with the Kimwipe.
19. Gently but firmly insert the nozzle into the small end of the PL-chip reservoir. Make sure that the nozzle is snug and there are no gaps or air bubbles between the nozzle and the reservoir.
20. Place the nozzle assembly in the reservoir holder, making sure not to kink the oil line.
21. Wet pipette 320µl of Hirudin blood into the reservoir.
    a. If the blood has been sitting for longer than a few minutes, gently pipette up and down 3-4 times to mix.
    b. Hold the pipette at an angle, roughly 2/3 of the way down to the bottom of the reservoir, touching the tip to the reservoir.
    c. **Slowly** expel the blood so that it runs down to the bottom of the reservoir so that there are no bubbles between the nozzle opening and the blood surface. If there are bubbles **do not proceed**.
        i. Bubbles in the reservoir impact the pressure distribution in the reservoir. In case of bubbles:
            1. Use the eye of a darning needle to scoop out small bubbles.
            2. Use a p10 or p20 pipette to deflate larger bubbles.

3. If unable to remove bubbles, remove the blood from the reservoir, discard the reservoir, and start again.

22. Remove the assembly from the holder, holding the reservoir in one hand and an overcap in the other.
    a. This typically works best when the overcap is held in your dominant hand.
23. Hold the overcap at a slight angle to the reservoir and insert into the reservoir opening, again avoiding bubbles.
    a. Holding the overcap at an angle significantly reduces introduction of bubbles.
24. Press the overcap firmly into the reservoir so that the lip of the reservoir is flush with the lip of the overcap. Excess blood should flow into the detachable part of the overcap, preventing the introduction of bubbles inside the capped reservoir.
25. Twist the overcap while still pressing down, then gently pull the detachable portion of the overcap off while continuing to twist. The chamber holding the excess blood should come off easily.
26. Using the lip of the detached chamber, scrape off any blood that may ooze out of the reservoir/assembly opening so that the blood is flush with the opening, then discard the detached chamber.
    a. If a large amount of blood remains, use a kimwipe to wick it away.
27. Position the reservoir assembly over desired chip channel, centering it over the opening. Make sure to hold the sides of the reservoir and NOT the nozzle connection.
28. Once the assembly is lined up correctly, press the reservoir straight down in one smooth motion, firmly and without twisting, so that the reservoir is snug and flush inside the chip opening.
29. Double check that all connections are flush and there are no bubbles in the system.
30. Begin the test.
    a. Click the “Start” button in the center of the application window.
        i. A window will appear reminding you to check the oil supply volume. Click “OK.”
    b. Click the “Start Recording” button at the bottom right of the application window.

31. Blood will begin flowing through the test channel, the timer on the camera will turn red and start counting up, and pressure data will be displayed in the graph window.
    a. Accidentally centering the camera over the wrong channel will not impact flow pressure data, as long as the test channel has not been used previously.
    b. You may reposition the camera at any time during the test without interrupting pressure data collection.
32. When base kPA +10 is reached, the time will be displayed in the T10 field (usually around 3 minutes).
33. The test will continue until either of two conditions are reached:
    a. Total pressure exceeds base kPa + 60 (occlusion threshold)
        i. "Measure Result Status" field will say "Complete: Run up to Occlusion Pressure"
    b. Ten minutes has passed without the occlusion threshold being reached.
        i. "Measure Result Status" field will say "Complete: Time up to AUC Time"
34. When the test is completed, the screen will flash once, the timer will stop and turn grey, the AUC10 at the bottom of the application will display the final AUC, and the "Measure Result Status" field will say "Complete:" with a message indicating which stop condition was met.
    a. It is easy to mistake whether the test is complete since blood usually continues to flow for some time after the test is complete, so be sure to check that the final AUC is displayed and the Measure Result Status" field with displays "Complete:" message before continuing.
35. Gently remove the reservoir from the chip, and then remove the reservoir from the nozzle.
    a. It is necessary to disassemble the test setup in this order to prevent blood from leaking.
36. Discard the used reservoir and return the nozzle to its holder.
37. If both channels of the chip have been used, slide the camera arm and discard the chip. Otherwise, leave the chip in place for the next test.

38. Test data will automatically save, and you may proceed to the next test. If you are done for the day, proceed to shutdown procedure.

T-TAS shutdown: PL-chip

1. Dispense a small amount of oil from the nozzle to make sure the tip is clean by pressing the "OIL" button on the front of the T-TAS unit.
2. Using a Kimwipe, wipe the excess oil from the nozzle, and place the nozzle in its holder.
3. Return the focus chip to the test platform, making sure to line up the pins on the platform with the holes in the chip.
4. Slide the camera arm down to the lowered position.
5. Fill the oil tank, as in step 10 of the Machine Startup section.
6. Once the oil tank is filled, close the application.
7. A window will pop up with the text "Cleaning EDTA Path with H2O is recommended. Time required: 20(sec)."
    a. Click "Cancel," since the PL-chip process does not use EDTA.
8. Another window will open asking "Are you sure that the tube is free of EDTA?"
9. Click "Yes."
10. The application will close. After about 20 seconds, the camera light on the T-TAS machine will start flashing.
11. Flip the power switch to the "Off" position. At this point you may hibernate/shut down the laptop.

Plasma and Whole Blood Viscometry

Machine footprint: 13"L x 13"W x 9"H

Time (per sample): ~2 minutes

Time (startup/walk away/shutdown/cleaning): ~20 minutes incubation time; personnel are free to do other things during this time

Note: It is possible to run the viscometer using the built-in keypad on both the measurement unit and the heating unit. This protocol uses the software provided by the manufacturer at time of instrument purchase. Please refer to the machine's user manual for keypad instructions.

Note: If testing both plasma and whole blood, the manufacturer recommends running all of the plasma samples first, then running all of the whole blood samples.

1.) Turn on both the small viscometer unit and the larger heating unit.
2.) Press the temperature control "On/Off" button on the heating unit to enable heating function.
3.) In the microVISC Control software, click the "Temperature" tab and set the temperature to 37°C. Make sure to click "Set," otherwise the unit will not heat.
    a. You may also wish to adjust the "Minimum Stability" and "Stability Window Length" parameter settings, as the default is fairly restrictive for practical use
    b. It may take 10-15 minutes for the unit to reach the desired temperature.
4.) Load the sample pipette by inserting it into the test liquid (either whole blood or plasma) and slowly pulling up on the plunger.
    a. Take care not to over-fill the pipette. Doing so will extend the plunger too far back, and the pipette will not fit into the test area.
    b. Once pipette is loaded, handle only by the flange.
        i. Holding by the barrel may cause unwanted heat transfer.
        ii. Holding by the plunger may cause accidental ejection of fluid or introduction of bubbles.
5.) Check the pipette for bubbles. If bubbles are present, hold the pipette vertically with the tip facing upwards, and gently flick the side of the pipette until the bubbles rise to the top. Press the plunger just enough to push the bubbles out of the pipette.
6.) Wipe the excess liquid from the outside of the pipette with a lint-free wipe to prevent particulate from being introduced into the test chamber.
7.) Mount the pipette into the viscometer by placing the tip at the inlet port and pressing down on the flange until it clicks into position.

a. Securing the flange takes a fair amount of pressure. Keep pressing until you hear it click.

8.) Close the lid of the heating unit, and double check that the temperature setting is correct.

9.) Allow the loaded sample to reach the test temperature (37°C).
    a. Manufacturer recommends an equilibration time of 20 minutes.

10.) In the "Operate" tab, enter desired test parameters using the "Measurement Mode" dropdown menu, then entering parameters where applicable.
    a. System defaults to "Automatic." All test parameters will be determined by the machine's internal measurements.
    b. "Advanced" allows user to define several parameters. Leaving a field blank or entering "0" will result in an automatic determination for that parameter. Definable parameters include:
        i. "Rate Values" -shear rate.
        ii. "Priming Volume"- volume of sample used to prime the system before measurement begins.
        iii. "Pausing Time"- time elapsed between end of priming step and start of measurement step.
        iv. "Measurement Volume"- volume of sample used to determine viscosity measurement.
    c. "Cleaning" initiates a cleaning cycle. In most cases, this is not necessary at instrument start-up.

11.) Double check that the temperature is stable, then click "Start."
    a. Do no open the lid or touch the sample until the sample is done running.

12.) Test data is automatically saved and may be accessed via the "Data" tab.

13.) Once the measurement is complete:
    a. If you wish to do so, AND there is sufficient volume remaining in the pipette, you may run another test on the sample. To do so, adjust the test parameters (if desired) and click "Start." If you wish to repeat the run with the same parameters, simply click "Start."

i. This process may be repeated until the volume remaining in the pipette is insufficient to continue.

b. Once the final measurement is completed, open the heating unit lid and press down on the metal lever next to the pipette flange to release the pipette.

14.) Discard the used pipette. Reloading/reusing may result in inaccurate or inconsistent results.

15.) Once the used pipette has been removed, there are several choices:

a. If you are running the another of the same sample type, return to step 3.

b. If you are running another sample that is a different type but is of similar viscosity, return to step 3 WITH THE EXCEPTION that you must discard the first reading due to sample mixing that may skew results.

i. Example: If completed sample was PRP, but the next sample will be whole blood, discard the first reading on the whole blood sample.

c. If you are going to test a sample of significantly different viscosity, perform a cleaning cycle (see next step) before continuing.

i. This is not an issue for switching between whole blood and plasma.

d. If you have completed measurements for the day OR it will be more than 1 hour before the next sample is tested, proceed to the next step.

16.) Run a cleaning cycle.

a. If more samples are going to be run:

i. Fill a pipette with Aquet detergent (1%) and mount as in steps 3-6 above.

ii. Select "Cleaning" from the "Measurement Mode" tab and click "Start."

iii. Once cycle is complete, return to step 3 to run next sample

b. If sample testing is complete:

i. Dampen a lint-free wipe with Aquet detergent (1%) and wipe excess sample from around the inlet port.

ii. Dip a lint-free swab in the Aquet solution and wipe the interior walls of the sensor cartridge inlet.

iii. Fill a pipette with the Aquet solution and mount as in steps 3-6 above.

iv. Select "Cleaning" from the "Measurement Mode" tab and click "Start."

v. Once cycle is complete, leave the empty pipette in the machine until the next time the instrument is used.

17.) Once the final cleaning cycle of the day is complete, switch off both machines.

18.) Empty the waste container and clean with your lab's preferred disinfectant and biocide. (The Framingham Heart Study uses CaviCide, but any disinfectant suitable for use in a BSL2 lab is fine.)

Flow Cytometry Protocols

Whole Blood Platelet Counts

Preparation:

1. Let Hirudin blood sit undisturbed for 30 post-draw.
2. Gently invert 6 times to mix and pipette 100 µL into a separate 2mL tube
3. Prepare 1x BD FACS Lysing Buffer in DI water from the 10x stock. (2mL per sample).
4. Prepare antibody mixture as follows:

   2.5µL CD61 antibody

   10.0µL CD45 antibody

   10.0µLCD14 antibody

   277.5µL Staining Buffer

Sample Treatment:

1. Add 2mL diluted lysis buffer to the microfuge tubes containing 100µL whole Hirudin.
2. Cap the tube and vortex until mixed, 2-3 seconds.
3. Incubate tubes at room temperature for 15 minutes.
4. Spin for 5min at 500rpm at max acceleration/deceleration.
5. Pipette off and discard the supernatant.
6. Resuspend pellet in 1mL Stain Buffer.
7. Cap the tube and vortex until mixed, 2-3 seconds.
8. Incubate at room temperature for 10 minutes.
9. Spin for 5min at 500rpm at max acceleration/deceleration.
10. Pipette off and discard the supernatant.

11. Resuspend pellet by pipetting in 300µL of antibody mix. Do not vortex.
12. Transfer mixture into an appropriately labeled flow tube.
13. Samples may now be run on the flow cytometer.
    a. Slow speed
    b. Run with Limits: 10,000 events

ADP Stimulation Assay

Preparation:

1. Prepare antibody mixture as follows (this formula will make enough mix for one flow sample).

    2.5µL CD61 antibody
    2.5µL CD63 antibody
    10µL CD62 antibody
    10µL PAC-1 antibody
    25µL PBS

2. Prepare fixation buffer. You will need 1150µL stain solution per flow sample. Calculate the total volume needed and prepare it as follows:

    1 part Cytofix
    3 parts Stain Buffer

3. In separate 2mL tubes, make a 1:40 dilution of PRP and whole blood (WB) in PBS (10µL sample + 390µL PBS).
    a. Let Hirudin blood sit undisturbed for 30 post-draw, then gently invert 6 times to mix before pipetting.
    b. PRP should be pipetted out of the spun sodium citrate tubes and combined prior to this step (see PRP/PPP Preparation protocol). Invert PRP tube once to mix before pipetting,
4. Flick tubes to mix.
5. For each participant, label four 5mL round-bottom flow tubes as follows:
    a. PRP+NS
    b. PRP+ADP
    c. WB+NS

d. WB+ADP

Sample Stimulation:

1. Add 5µL of Normal Saline to each of the tubes labeled “NS.”
2. Add 5µL of 200uM ADP to each of the tubes labeled “ADP.”
3. Add 45µL of diluted and mixed PRP to each of the tubes labeled “PRP.”
4. Add 45µL of diluted and mixed whole blood to each of the tubes labeled “WB.”
5. Cap the tubes and gently swirl or tap the tubes to mix.
6. Incubate on a dry heat block at 37°C for 15 minutes.
7. Remove tubes from the heat block, and add 50µL antibody mix.
8. Return tubes to the 37°C heat block for 15 minutes.
9. Remove tubes from the heat block, and add 1150µL staining solution mix.
10. Samples may now be run on the flow cytometer.
    a. Slow speed
    b. Run with Limits: 10,000 events

Optimul plate-making protocol

Part one: Gel coating

1.) Prepare gel coating solution, using Table 1 as a guide. Select the number of plates needed, and use the masses/volumes in the corresponding column to make the gel coating solution.
    a. Make Buffer A: Monobasic NaH_2PO_4 monohydrous in DI water
    b. Make Buffer B: Dibasic Na_2HPO_4 anhydrous in DI water
    c. Combine buffers A and B, then dilute with DI water to make Buffer C.
    d. Add gelatin and Tween 20 to buffer C
    e. Stir at 500rpm for 20 minutes before use
2.) Pipette 150uL of gel coating solution into required wells. It is not necessary to gel coat wells that will not be used when adding agonist or running sample.
3.) Let plates sit, undisturbed, at room temperature for at least 4 hours.
4.) Wash plates 2x with 0.01% Triton X-100

5.) Wash plates 2x with DI water.
    a. It is recommended to use a plate washer for steps 4 and 5, however washes may be done by hand. If washing by hand, wash 3x with water to ensure complete removal of the Triton solution.
6.) Let plates air dry overnight at room temperature.
    a. Plates may be stacked to conserve space. If stacking, stagger plates to allow airflow. Additional dry time may be required.
7.) Plates should be stored covered to prevent dust/detritus from settling into the coated wells.
8.) Gel coated plates are stable for 6+ months before adding agonist.

Part two: Adding agonist

1.) Prepare required buffers
    a. 25ml of 0.1% ascorbic acid in PBS.
    b. 4ml of 0.1% ascorbic acid in DI water.
    c. 4ml of 0.1% ascorbic acid in Ethanol.
    d. 4.4ml of 0.1% ascorbic acid, 0.18% glucose, 5% human serum albumin (HSA). This should be done stepwise.
        1. Add 9mg glucose to 5ml of 0.1% ascorbic acid and invert to dissolve.
        2. Add 220mg HSA to 4.4ml of above and gently invert to dissolve, avoiding bubbles.
2.) Prepare agonist working stock solutions (Table 2, columns B & C).
    a. Exclude Arachidonic Acid. To prevent agonist oxidation, this must be the last agonist pipetted into to the test plates and must be prepared immediately before pipetting.
3.) Pipette buffers for dilution into a deep-well 96-well plate ("dilution plate").
    a. Appropriate buffer found in Table 2, column D.

b. To row A of the 96-well plate, add the volume of buffer found in Table 2, column E
c. To rows B through H of the dilution plate, add the volume of buffer found in Table 2, column G.

4.) Add the appropriate volume (Table 2, column F) of agonist working stock to row A of the dilution plate, pipetting up and down 4-5 times to mix thoroughly.
5.) Perform serial dilutions by pipetting the appropriate volume (Table 2, column H) from dilution plate row A into row B and pipetting up and down 4-5 times to mix thoroughly, and so on, stopping at row G.
    a. Do *not* add agonist to row H, as the wells in row H are used as blanks to remove background signal.
6.) Spin the dilution plate briefly (5-10 seconds using the "short" or "pulse" button on the centrifuge) to collect all solutions at the bottom of the wells.
7.) Using an electronic multichannel pipette, add 5ul of agonist to the corresponding position on the experimental plates, being careful to pipette the liquid into the bottom of the wells.
8.) Once all agonists have been pipetted, prepare the Arachidonic Acid agonist in the same manner as the rest of the agonists with the following two exceptions:
    a. The working stock is used as the top well dilution, rather than making a separate dilution.
    b. Do *not* spin the dilution plate after agonist preparation is complete. It is unnecessary for Arachidonic Acid since it is in ethanol and allows more time for agonist oxidation and ethanol evaporation.
9.) Pipette agonist as in step 7.
    a. Pipetting the diluted agonist up and down 2-3 times before pipetting into the plates. This serves 2 functions
        i. Mixes the agonist. Arachidic acid does not go into solution well in ethanol. Mixing prior to pipetting helps ensure consistency across all plates.
        ii. Prevents agonist dripping out of the pipette tips while in-process due to the low surface tension of ethanol.

10.) Gently stack the plates into stacks of 5-7 plates each and place in a -80°C freezer.
    a. Place a clean piece of aluminum foil on the freezer shelf before placing the plates inside to prevent freezer "snow" collecting on the bottom of the plate.
    b. Cover the plates with a clean piece of aluminum foil to prevent freezer "snow" falling into the wells.
11.) Freeze the plates at -80°C for 2-4 hours.
12.) About 20 minutes before removing the plates from the freezer, turn on the lyophilizer (freeze-drier) to allow it to reach -40°C or lower.
13.) Remove the plates from the freezer and stack them in the lyophilizer.
14.) Turn on the pump and close the vacuum valve on the lyophilizer. Test that a vacuum is being generated by pulling up on the lid.
15.) Lyophilize the plates for 8 hours or overnight.
16.) Release the vacuum valve, turn off the pump, and *carefully* remove the plates from the lyophilizer. At this point, the agonist can easily become dislodged from the side of the wells, causing it to jump into other wells or out of the plate entirely. To prevent this kind of damage:
    a. Only handle the plates by the sides or the end that does not have agonist.
    b. DO NOT touch the bottom of the plate.
    c. Be careful not to drop, jostle, or rattle the plates in any way.
17.) Vacuum seal each plate individually, while continuing to handle carefully.
    a. Hold the vacuum bag open as much as possible when sliding the plate inside.
    b. Try not the move the plate around once it is in position.
18.) Once all of the plates are sealed, wrap them in aluminum foil and store them at room temperature until use.
19.) Plates expire 12 weeks after being prepared. Do not use them past expiry.

Table 1

Solution	Ingredients	Unit of Measure	40 Plates	60 Plates	80 Plates	90 Plates
Buffer A	Monobasic NaH2PO4 monohydrous	mg	110.4	165.6	220.8	248.4
	DI water	mL	40	60	80	90
Buffer B	Dibasic Na_2HPO_4 anhydrous	mg	568	852	1136	1278
	DI water	mL	200	300	400	450
Buffer C	Buffer A	mL	38	57	76	85.5
	Buffer B	mL	162	243	324	364.5
	DI water	mL	200	300	400	450
Gel Coating Buffer	Buffer C	mL	400	600	800	900
	Gelatin	g*	3	4.5	6	6.75
	Tween 20	µL**	200	300	400	450
*Note that this is g, not mg.						
**Note that this is µL, not mL.						

Table 2

Column A	Column B	Column C	Column D	Column E	Column F	Column G	Column H
	Working Stock Dilution			Top Well Dilution		Subsequent Dilutions	
Agonist	Amount of Agonist	Volume & Diluent	Buffer for Plate Dilution	Buffer (µL)	Stock (µL)	Buffer (µL)	Previous (µL)
Arachadonic Acid	1 Vial	1026.4 µL EtOH	Ethanol +0.1% Ascorbic Acid	Use "Working Stock Dilution"		385.5	514.5
ADP	1 Vial	100µL DI water (need 2 vials)	PBS + 0.1% Ascorbic Acid	340	160	333.4	66.6
Collagen	1 Vial	950µL PBS + Glucose + HSA[ǂ]	PBS + Glucose + HSA + 0.1% Ascorbic Acid	476	224	375	125
Epinephrine	1 Vial	500µL H2O	PBS + 0.1% Ascorbic Acid	460	40	300	66.6
Ristocetin	15mg Vial	375µL Saline (need 2 vials)	H2O + 0.1% Ascorbic Acid	115	460	250	333.6
TRAP-6	1 Vial	150µL Saline (need 2 vials)	PBS + 0.1% Ascorbic Acid	340	160	350	155.4
U44619	Frozen Aliquot[♯]	Frozen Aliquot[♯]	PBS + 0.1% Ascorbic Acid	340	160	300	85.6
PAR4	1mg	1.469mL PBS	PBS + 0.1% Ascorbic Acid	450	300	210	525

[ǂ]HSA- Human Serum Albumin; NS- Normal Saline

[♯] U46619 agonist comes as a pre-diluted stock at 10mg/ml. Dilute 11.2µL of stock agonist in 20.8µL ethanol. Remove 30 µL to a separate tube and dilute in 968µL PBS with 0.1% ascorbic acid. Dispense into 165µL aliquots and store at -80°C until use.

Optimul 96-well plate assay.

Machine (plate reader) footprint: 18”L x 15”W x 6”H

Machine (orbital plate shaker) footprint: 7”L x 6”W x 4”H

Time: ~8 minutes/per sample (once PRP and PPP plasma isolated from centrifugation)

Preparation:

5. Turn on the Optimul plate reader. It will perform a self-check and make a series of grinding and clicking noises. This is normal.
6. Turn on the heated orbital plate shaker and set to 37C.
    a. Switch on.
    b. Press the + symbol above the word “temp” until the display reads 37C.
    c. Press start.

Sample Processing:

14. Unwrap the foil on a pre-made, agonist coated 96-well plate.
15. Examine the plate for any loose or missing agonist. Discard damaged or incomplete plates.
16. Remove the vacuum-sealed wrapping and re-inspect the plate.
17. Pour the PRP to be tested into a reagent trough.
18. Using a multichannel pipette, wet pipette 40µL of PRP into plate columns 2-8, rows A-H.
    a. Wet pipetting may also be referred to as “reverse” pipetting. This is done to prevent the addition of excessive bubbles.
19. Using a single channel pipette, wet pipette 40µL of PRP into well 1E.
20. Wet pipette 40µL of PPP into wells 1A-D, being careful not to disturb the red cell layer in the draw tubes.
21. Gently tap the plate on the counter to make sure all liquid is on the bottom of the wells.
22. Examine each well for bubbles. Scoop any bubbles out of the well with the eye of a darning needle.
23. Stir the top 2 wells of the Risto row, since they have a tendency not to dissolve completely otherwise.
24. Read the plate at 595nm on a plate reader.
    a. Because this protocol requires a starting and ending plate read, it is ideal to create a protocol using the plate reader software to handle the reads
25. Once the read is complete, place the plate on the orbital shaker and shake for at 37C for 5 minutes at 1,200 RPM
26. When the incubation is complete, remove the plate and check it again for bubbles and debris.
    a. You may wish hold the plate at a steep angle and tap the side to help aggregates fall to one side of the well so that it does not interfere with scanning.
27. Return the plate to the scanning tray, and re-read at 595nm.
28. Export the file to an Excel file.
29. Run the Excel macro, which is designed to format the data for easy analysis, and save the resulting sheet as a .csv (comma delimited) file.

30. Make sure to save the read file from the plate reader before closing.
31. Repeat the "Sample processing" procedure for each participant.

Unused/leftover sample handling

PRP- saving for future RNA studies

Time: 10 minute spin, then ~2 minutes /per sample. Personnel free to work on other things during spin.

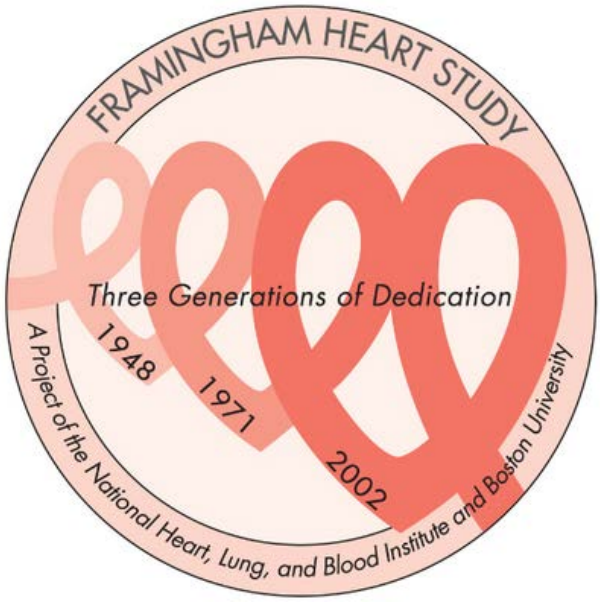
1.) Pipette unused sample PRP into a 2mL screwcap freezer tube. Split between multiple tubes as necessary. Be sure to label tubes.
2.) Spin samples for 10 minutes at 1,000 RCF.
3.) Remove and discard supernatant.
4.) In a fume hood, resuspend pellet in 1mL TRIzol reagent. Pipette carefully to completely resuspend.
    a. TRIzol is a highly toxic carcinogen and can penetrate nitrile gloves. Handle with care and remove contaminated gloves immediately.
5.) If you have multiple tubes from the same sample, there are 2 options regarding how sample is saved.
    a. Pipette 1mL TRIzol into each tube and resuspend pellets separately for storage separately.
    b. Pipette 1mL TRIzol into one tube and resuspend. Once pellet is resuspended, remove liquid into the next tube and resuspend pellet in the same TRIzol as the first. Be sure to remove all liquid from the first tube.
6.) Make sure the screwcap is closed tightly, and store samples at -80°C until needed.

PPP- saving for future ELISA studies

Time: ~1 minute /per sample

1.) Pipette unused sample PPP into two 2mL screwcap freezer tube, split evenly between each tube. Be sure to label tubes.
2.) Make sure the screwcap is closed tightly, and store samples at -80°C until needed.

Framingham Heart Study



Brain Health Station

Hearing Examinations MOP

Offspring Cohort Exam 10 & OMNI Cohort Exam 5

Table of Contents

Scheduling and Pre-Test Instructions

Scheduling of participants for the clinic test site is accomplished by the FHS Core Recruitment Team, with details communicated to research assistants and Audiology weekly. At the time of the scheduling contact, participants will be informed of the intent to test hearing and that it can be done only if there is not too much ear wax. If the participant wears hearing aids, or if they have known trouble with cerumen accumulation, they may wish to have this checked/removed before their visit. Scheduling for participants requiring remote testing will be arranged with Audiology's input to assure staff availability.

Forms, SOPs, Equipment Manuals, Support Numbers

Hard copies on site and additionally available on the Exam 10 OneDrive file for electronic access.

Daily Start-up Activities

To be performed before assessments begin each day:

1. Obtain daily schedule sheet with participant information
2. Obtain all necessary equipment, including otoscope, tympanometer, headphones, tablet and sound level meter.
3. Gather disposable otoscope tips, disposable tympanometry tips, disinfectant wipes, gloves, masks.
4. Gather Standard Operating Procedure (SOP) notebook with Appendices and all forms that may be needed for set-up and testing:
    a. **Hearing Evaluation Form** (Appendix A; one for each participant)
    b. **Equipment Log** (Appendix D; one)
    c. **Medical Referral Forms** (Appendix E, 3 versions, multiple copies)
5. Set up equipment and perform daily function checks (see Appendix C: '**Calibrations and Daily Function Checks'**). Report any concerns immediately to supervising audiologist. Confirm completion and outcome of daily function checks on the **Equipment Log** (Appendix D). Supervising audiologist to review entries weekly in absence of reported problems.

Greeting and Description of Hearing Assessment Procedures

1. The participant will be escorted to/arrive at the hearing test area within the clinic. The tester will greet the participant and seat them at the designated test location. The door to the examining room will then be closed.
2. The tester will provide a clear and brief explanation of the procedures (otoscopy, tympanometry, audiometry) to be accomplished. This should be done face to face, with hearing aids on, if they are worn.
3. After this introduction, the tester will ask the participant if they have any questions/concerns regarding the tasks to be accomplished, will address these, and will then proceed with the evaluation.
4. At this point, the tester also will instruct the participant to remove hearing aids or other hearing devices, as well as headbands, eyeglasses, large earrings, or anything that may interfere with proper positioning of earphone cushions on the ears.

Testing Procedures

A. Otoscopy

- A.1. Overview: The goal of this inspection is to identify conditions (potentially occluding cerumen) that may interfere with establishment of accurate hearing thresholds, or that signal the presence of active disease that may contribute to abnormal test results and suggest need for medical follow-up.
- Using an illuminated otoscope and disposable ear tip of appropriate size, the tester will inspect, bilaterally, the external ear canals and tympanic membranes for gross integrity; i.e. confirm that there is no obviously occlusive cerumen, obvious tympanic membrane perforation, or drainage from the canal.
- A.1.1 Equipment needed: Welch Allyn Otoscope (illuminating head and rechargeable base/handle)
- A.1.2 Supplies needed: Disposable speculae (ear tips), disinfectant wipes
- A.2 Otoscopy procedure: The tester will be gloved. Place a new speculum on the otoscope. Turn on the otoscope light. Explain to the participant, face to face, that you are going to look in their ears and that they should sit quietly while you do so. Starting with the right ear, pull up and back on the participant's outer ear (pinna) in order to straighten the ear canal. It is important to brace the hand holding the otoscope against the patient's head to avoid injury to the ear canal by placing the little

finger against the head. Gently direct the otoscope into the ear canal and observe the canal and ear drum. The scope may be tilted in order to see the entire drum. Tilt the top of the patient's head away from you slightly and rotate their head away slightly to improve the view.

Complete this for both the right and left ear and record the on the **Hearing Evaluation Form** (Appendix A).

Dispose of the soiled ear tip and use a disinfectant wipe on the otoscope.

- Unusual/Abnormal findings. Foreign objects in the ear canal, drainage: If either are observed, tympanometry and audiometric testing are not conducted. Soft cerumen is not to be confused with active drainage.
- Occlusive cerumen. Occlusion/patency of canal suspected by visual inspection may be confirmed by tympanometry (flat configuration, abnormally small volume) if it can be accomplished.
    - Mark unusual/abnormal findings on Appendix A and a letter will be sent to the participant's PCP.

B. Tympanometry

- B.1. Overview: Middle ear pathology alters sound transmission through the middle ear to the inner ear and thus impacts effective stimulation of the cochlea. Its presence can be temporary; what is present today may not permanently impact hearing. It can also compromise interpretation of other tests of auditory function. It is therefore important to assess the function of the middle ear in conjunction with the tests of hearing.
- B.1.1 Equipment needed: Interacoustics Titan Tympanometer, Titan calibration cavity
- B.1.2 Supplies needed: Disposable tympanometer ear tips in a variety of adult sizes, disposable wipes, gloves, masks
- B.1.3 Calibration: The tympanometer needs to be turned on and calibrated each morning before testing can be done. Two 'calibration cavities' are provided for this purpose. See Appendix C: '**Calibrations and Daily Function Checks'** for start-up and calibration procedures.
- B.1.4 Participant Information: Enter relevant participant information into the Titan Neuro ID only

- B.2 Tympanometry procedure: The tester will be gloved. Instruct the participant (face to face): "This is a test to measure how well your eardrums move. It is a completely automatic test, so you don't need to respond in any way. I am going to place a probe (show it to them) snugly into the opening of your ear canal. You will hear a sound and will feel some small changes in pressure. It is important that you do not move, speak or swallow until the test is finished. It should take about 30 seconds. Do you have any questions?"

  Tympanometry will be performed in both ears of the participant. Begin with the right ear. Grasp the outer ear (pinna) and pull up and back in order to straighten the ear canal. 'Scoop' the tip in position behind the small flap of skin (tragus) at the bottom of the ear canal opening. The angle of the probe in the canal should be the same as used when inspecting the eardrum by otoscope. The probe needs to be secure enough in the canal to allow a pressure seal to be created beyond it.

  With the probe tip in the external ear canal, activate the system's pressure check. After assurance that an adequate pressure seal has been achieved (display arrow on screen), the device will automatically vary ear canal pressure and stimulus to the ear. If the pressure test fails, reposition the probe to improve the seal and repeat the pressure check. The Titan device will capture and store the relevant data. When there is no peak pressure, compliance is < 0.3cm^3, and ear canal volume < 0.6ml, the result suggests occluding cerumen. Likewise, volumes > 2.5 ml are consistent with tympanic membrane perforation. Both conditions suggest medical referral.

  Repeat the procedure for the left ear.

  Dispose of the soiled ear tip and use a disinfectant wipe on the probe that couples to the ear.

- B.3. Could not test: If the test cannot be completed, please note the reason on the **Hearing Evaluation Form** (Appendix A).

  Test data for each participant should be uploaded at the end of each session as described at the end of this document, in '**Data Uploads and Storage'.**

C. Audiometry

- C.1. Overview: Pure tone audiometry is used to determine the participant's hearing thresholds. For this study, a tablet based audiometer with a wireless Bluetooth headset will be used to allow portability of the testing to multiple remote sites while maintaining high sound isolation.

- C.1.1 Equipment needed: Creare audiometer/headset, Samsung tablet, Svantek sound level meter
- C.1.2 Supplies needed: Disposable wipes
- C.1.3 Calibration: The headset/tablet system needs to be turned on and a function check performed each morning before testing can be done. See Appendix C: '**Calibrations and Daily Function Checks'** for start-up and calibration procedures.
- C.1.4 Participant Information: Enter relevant participant information into the tablet
  De-identified Neuro Group ID's, Tech ID of RA, Age of "0", Gender of "Other", Location "FHS"

C.2 Audiometry procedure: The participant will remain seated. Seating will be arranged to: i) avoid giving inadvertent visual cues to the participant, ii) enable easy observation of participant responses to stimuli, iii) allow for the monitoring and reinforcement of responses and iv) permitting observation of participant comfort, safety, and health. This can be achieved with the participant seated perpendicular to the tester.

The test instructions should be delivered face to face and presented in a manner appropriate for the participant and shall accomplish the following:

- Indicate the purpose of the test, that is, to find the faintest tone that can be heard.
- Emphasize that it is necessary to sit quietly, without talking, during the test.
- Indicate that the participant is to respond (hand/finger raise) whenever the tone is heard, no matter how faint. Note: Individuals sometimes wish to/need to verbalize (say 'yes' when they hear the tone) instead. Vocalizing should be avoided if possible, but if not possible, accept verbal responses.
- Indicate that each ear will be tested separately with tones of different pitches.
- Provide an opportunity for questions the participant may have.
- Prepare the participant (no moving, talking) and record a 10 second sample of room ambient sound level using the noise-logging dosimeter

The tester should then place the earphones on the participant (**RED on the right ear** and **BLUE on the left ear**) and adjust them to fit the head properly. Do not allow the participant to place or adjust the headphones. Testing will be performed in both ears of the participant. Begin with the right ear.

The basic procedure for threshold determination consists of (a) familiarization with the test signal and (b) threshold measurement. The purpose of familiarization is to assure the tester that the participant understands and can perform the response task, and for the participant to hear the type of sound they will be listening for. For this study, familiarization will take place at the beginning of the right ear testing and again when beginning to test the left ear.

Familiarization: Present a 1000-Hz tone at a 30 dB hearing level (HL). If a clear response occurs, begin threshold measurement. If no response occurs, increase the tone level to 50 dB HL, and then at successive additional increments of 10 dB until a response is obtained. At this point threshold determination can begin.

Threshold measurement: Test tones should be 3-4 seconds in duration, with inter-stimulus interval varied throughout testing to discourage patterned responses. Following the familiarization, the tester will lower the test tone level in 10 dB steps until there is no response to the presentation. When that occurs, increase the tone level in 5 dB steps until there is a response. Once a response is obtained, again lower the level by 10 dB and increase by 5 dB until you have obtained responses to 2 of 3 presentations. (Threshold is defined as the lowest decibel hearing level at which responses occur in at least one half of a series of ascending trials. Thus, the minimum number of responses needed to determine the threshold of hearing is 2 responses out of 3 presentations at a single level). This lowest level of response is entered in the tablet as threshold at this frequency for this ear.

Repeat the process for the remaining frequencies to be tested. The test order for each ear is: 1000, 250, 500, 1000 (for test-retest reliability), 2000, 3000, 4000, 6000, and 8000 Hz. If the repeat measure for 1000 Hz differs from the first by more than 5 dB, reinstruct the participant. If the difference remains, continue testing. Note: Masking function is not available.

Repeat the procedure for the left ear.

- C.3. Could not test: If the test cannot be completed, please note the reason on the **Hearing Evaluation Form** (Appendix A).

Test data for each participant should be uploaded at the end of each session as described at the end of this document, in '**Data Uploads and Storage'.**

Medical Referrals and Notifications

Screening results will be communicated to participants and PCPs using letters found in the Appendix as follows:

The 'Normal' letter will be sent to the participant (only), when findings are unremarkable.

The 'Urgent' letter will be sent to the participant and the 'Urgent-PCP' letter will be sent to the PCP when a medical referral is made. This will occur with:

1. Participant report of sudden, recent (within 6 months) hearing loss
2. Otoscopic observation of:
    a) a foreign body in the ear canal
    b) excessive cerumen confirmed by tympanometry to be occlusive (see below)
3. Tympanometry consistent with:
    a) tympanic membrane perforation (ear canal volume more than 2.5 ml) or
    b) occlusive cerumen (ear canal volume less than 0.6 ml)

4) Asymmetric pure tone thresholds (≥ 25 dB HL at any two consecutive test frequencies (NHCA referral criteria) or ≥ 15 dB HL at 500 Hz, 1000 Hz, 2000 Hz and 3000 Hz (AAO-HNS criteria)

The 'Non-Normal' letter will be sent to the participant when there are intermediate findings:
For example, non-occlusive cerumen or threshold elevations commonly seen with age. Findings will be described but not directly referred for medical follow-up.

1. Thresholds greater than 25 dB HL at 1000 Hz, 2000 Hz, 3000 Hz or 4000 Hz
2. Non-occlusive cerumen

Data Uploads and Storage

Tympanometry Data: Data acquired during tympanometry testing with the Interacoustics Titan will be temporarily stored on the device. At the end of each day, these data should be uploaded to the Titan Suite downloaded on the FHS laptop. Weekly, all data should be secondarily backed up to the FHS NeuroExam10 Network drive (\\fhs-srv-neurdsk\NEUROExam10\Hearing_Data), confirmed at both storage locations and then removed from the handheld device. This also will allow QA to be performed by the supervising audiologist from the MEEI site.

Commented [KS1]: Need Tim/BU/FHS input here

Tablet Hearing Test Data: Data acquired via the Creare system are automatically uploaded to GitLab, a HIPAA compliant, secure cloud based data server, which also will allow QA to be performed by the supervising audiologist from the MEEI site.

End of day

1. Equipment power down, wipe down, charging, storage
2. Data uploads with confirmation as described above.

3. Communicate all testing concerns/abnormalities to Danielle.

Commented [KS2]: This will need additional detail once the Framingham group tells us where data are to be backed up

Off-Site Testing - TBD

Training Log

The research assistants (RAs) completed training on all aspects of the hearing component of the Brain Health Station. The goal of these trainings was to be competent in otoscopy, tympanometry and pure tone audiometry.

A summary of their training are included below:

1. Completed four, three to four hour in-person trainings over the course of two weeks. The majority of this time was hands-on practice with the relevant equipment. All aspects of testing were initially modeled by an audiologist and then practiced among the RAs.

2. Read and familiarized with provided written instructions and protocols for each aspect of testing.

3. Completed testing on participants with 100% supervision from an audiologist for one week. Reviews were completed following each participant seen. This time was also used to train on difficult to test participants, troubleshooting and data transfer. An additional two weeks were utilized for one research assistant for extra training with participants.

Equipment List

The Brain Health Station's hearing testing equipment includes the following:

1. Welch Allyn 25070-M 3.5v MacroView Otoscope Set: The otoscope allows the assessment of a participant's ear canal and ear drum. It utilizes disposable specula and plugs into the wall to charge.

2. Interacoustics Titan Tympanometer: The Titan allows the assessment of a patient's middle ear status, including ear canal volume, tympanic membrane compliance and middle ear pressure. It includes two calibration cavities and a desk stand.

3. Svantek SV 104A Noise Dosimeter: The dosimeter allows a measurement of the ambient noise in the testing room. It runs through the TabSINT application and plugs into the wall to charge. It also comes with a CD that allows access to computer software.

4. Samsung Galaxy Tab A (SM-T380NZKEXAR): The tablet houses the TabSINT application, which is utilized for the hearing test. It uses a microUSB to charge and plugs into a surge protector in the exam room.

5. Wireless Automated Hearing-Test System (WAHTS): This refers to the circumaural headphones that were included in the hearing system. They charge with a microUSB plugged into the left headphone and into the surge protector. WAHTS utilizes Bluetooth to connect to the TabSINT application via tablet.

6. Adjustable swivel chair for participant: The adjustable nature of the chair allows the participant to be easily moved for easier access to both of their ears during otoscopy and tympanometry, as well as to have them face away from the RA during the hearing test.

7. Standard chair for RA to sit at while administering hearing test.

Appendix A

Hearing Evaluation Form

Screening Questions

History of:	HEARING LOSS	TINNITUS	EAR FULLNESS	DIZZINESS
	EAR INFECTIONS	EAR SURGERY	SIGNIFICANT EAR WAX	
Hearing aid use?	NO	RIGHT	LEFT	BOTH

Otoscopy

Right Ear

Canal	CLEAR	NON-OCCLUDING WAX	OCCLUDING WAX	ABNORMAL
Ear drum	VISUALIZED	NOT VISUALIZED	ABNORMAL	

Left Ear

Canal	CLEAR	NON-OCCLUDING WAX	OCCLUDING WAX	ABNORMAL
Ear drum	VISUALIZED	NOT VISUALIZED	ABNORMAL	

Tympanometry

Right Ear

Able to complete	YES	NO	
If no, why?	CANAL ABNORMALITY	DRAINAGE	INADEQUATE PRESSURE SEAL

Left Ear

Able to complete	YES	NO	
If no, why?	CANAL ABNORMALITY	DRAINAGE	INADEQUATE PRESSURE SEAL

[Date]
[Participant Address]

Dear [Participant Name],

Thank you for your participation in the Brain Health Study, an ancillary study of the Framingham Heart Study. Your involvement in this study provides us with very important information to better understand how your eyes, hearing and walking can reflect the health of the brain. We hope you found it to be an interesting experience.

I am writing this letter as a summary of the results of your participation in the hearing exam component. During your visit we checked your ear canals and ear drums, checked the pressure of your middle ear, and screened your hearing with tones. The results of these tests appear unremarkable. Please note that these results are not intended for clinical use and do not replace evaluation and testing that may be recommended by your primary care physician, audiologist or ear, nose and throat (ENT) physician. If you have hearing-related concerns, we encourage you to contact your primary care physician for further advice about standard-of-care evaluations that may be appropriate for you.

The below websites are useful resources about ears and hearing. Feel free to brose these if you are looking for more information.

- *http://www.enthealth.org/* ENT Health, powered by American Academy of Otolaryngology-Head and Neck Surgery
- *https://www.asha.org/aud/pei/* Audiology patient education handouts from the American Speech-Language-Hearing Association

If you have any questions, please do not hesitate to call Tim Kowalczyk at 508-935-3410.

Thank you again for your continued support of the Framingham Heart Study.

Sincerely,

D. Bradley Welling, MD

[Date]
[Participant Address]

Dear [Participant Name]:

Thank you for your participation in the Brain Health Study, an ancillary study of the Framingham Heart Study. Your involvement in this study provides us with very important information to better understand how your eyes, hearing and walking can reflect the health of the brain. We hope you found it to be an interesting experience.

During your visit, we checked your ear canals and ear drums, checked the pressure of your middle ear, and screened your hearing with tones. These screens showed the following:

Include non-normal findings here.

Please note that these results are not intended for clinical use but may be useful for your primary care doctor or hearing care provider. You may wish to contact them for further information about any potential follow-up that may be appropriate.

The below websites are useful resources about ears and hearing. Feel free to browse these if you are looking for more information or looking to find an audiologist.

- *http://www.enthealth.org/* ENT Health, powered by American Academy of Otolaryngology-Head and Neck Surgery
- *https://www.asha.org/aud/pei/* Audiology patient education handouts from the American Speech-Language-Hearing Association

If you have any questions, please don't hesitate to call us. Please feel free to call Tim Kowalczyk at 508-935-3410.

Thank you again for your continued support of the Framingham Heart Study.

Sincerely,

D. Bradley Welling, MD

[Date]
[PCP Address]

Dear Dr. [PCP Name]:

Your patient, [Participant Name], has participated in an ancillary research study of the Framingham Heart Study. Their involvement in this research study provides us with very important information to better understand how eyes, hearing and walking can reflect the health of the brain.

I am writing this letter as a summary of the research results of their participation in the hearing exam component. Please note that these results are not intended for clinical use but we are providing them as a source of information for you to review in case you find any of the information useful. We have encouraged your patient to discuss these results with you and have also provided a copy of the results to the patient.

During the visit we performed otoscopy, tympanometry and pure tone audiometry. These screens showed the following:

Include abnormal findings here.

If you have any questions, please do not hesitate to call Tim Kowalczyk at 508-935-3410.

Thank you again for your continued support of the Framingham Heart Study.

Sincerely,

D. Bradley Welling, MD

[Date]
[Participant Address]

Dear [Participant Name]:

Thank you for your participation in the Brain Health Study, an ancillary study of the Framingham Heart Study. Your involvement in this study provides us with very important information to better understand how your eyes, hearing and walking can reflect the health of the brain. We hope you found it to be an interesting experience.

During your visit, we checked your ear canals and ear drums, checked the pressure of your middle ear, and screened your hearing with tones. Please note that these results are not intended for clinical use but may be useful for your primary care physician (PCP) or hearing healthcare provider. These screens showed the following:

Include abnormal findings here.

These findings appear abnormal and require review by your healthcare provider. We have notified your PCP regarding this screening. Please contact them for further information about any potential follow-up that may be needed.

The below websites are useful resources about ears and hearing. Feel free to browse these if you are looking for more information or looking to find an audiologist.

- *http://www.enthealth.org/* ENT Health, powered by American Academy of Otolaryngology-Head and Neck Surgery
- *https://www.asha.org/aud/pei/* Audiology patient education handouts from the American Speech-Language-Hearing Association

If you have any questions, please don't hesitate to call us. Please feel free to call Tim Kowalczyk at 508-935-3410.

Thank you again for your continued support of the Framingham Heart Study.

Sincerely,

D. Bradley Welling, MD

[Date]
[PCP Address]

Dear Dr. [PCP Name]:

Your patient, [Participant Name], has participated in an ancillary research study of the Framingham Heart Study. Their involvement in this research study provides us with very important information to better understand how eyes, hearing and walking can reflect the health of the brain.

I am writing this letter as a summary of the research results of their participation in the hearing exam component. Please note that these results are not intended for clinical use but we are providing them as a source of information for you to review in case you find any of the information useful. We have encouraged your patient to discuss these results with you and have also provided a copy of the results to the patient.

During the visit we performed otoscopy, tympanometry and pure tone audiometry. These screens showed the following:

Include abnormal findings here.

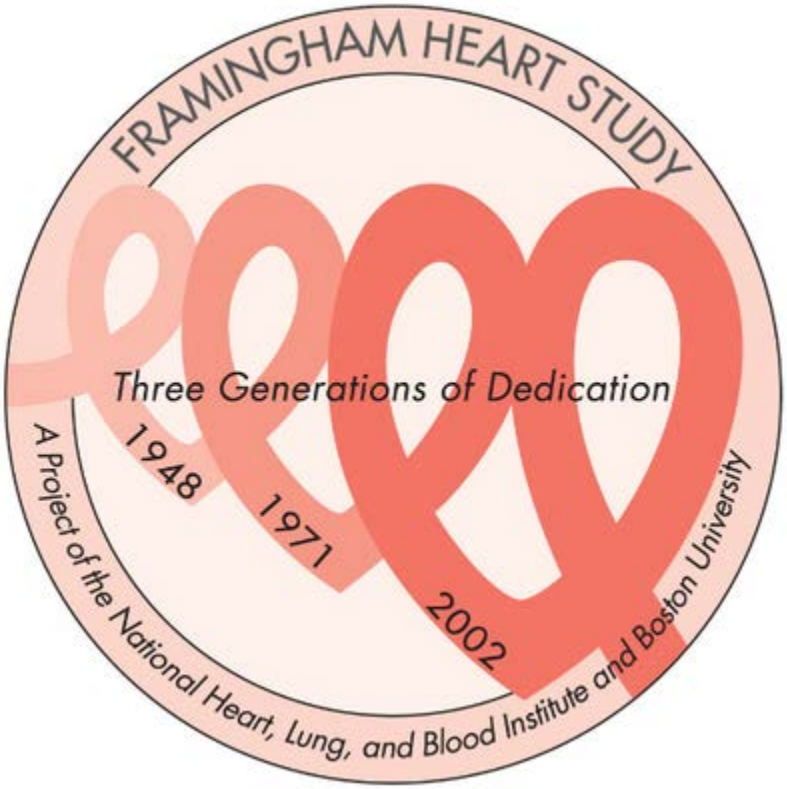
If you have any questions, please do not hesitate to call Tim Kowalczyk at 508-935-3410.

Thank you again for your continued support of the Framingham Heart Study.

Sincerely,

D. Bradley Welling, MD

Framingham Heart Study



Brain Health Station

Vision MOP for OCTA and IOL Master Equipment

Offspring Cohort Exam 10 & OMNI Cohort Exam 5

Table of Contents

Overview of Vision Testing for Brain Health Station:

Changes in both neurosensory retinal tissue and retinal vasculature have been noted in Alzheimer's Disease and Related Dementias (ADRD) as well as in cerebrovascular disease. Cross-sectional studies using optical coherence tomography and post-mortem studies have each demonstrated attenuation of retinal vessels, and atrophy of the retinal nerve fiber (RNFL) and ganglion cell layers in AD. Incidence of TIAs and strokes, risk factors for vascular dementia, correlates with focal atrophy of RNFL and macroscopic retinal vascular changes. There are reproducible correlations between large caliber retinal vascular features and markers of brain small vessel disease (SVD) such as white matter lesions (WML), lacunar infarcts, microbleeds, as well as poor cognitive performance. Clinically visible sequelae of retinal capillary damage (also referred to as "retinopathy"), such as retinal hemorrhages also correlate with cognitive performance and cerebral atrophy independently of vascular risk factors such as diabetes mellitus (DM) or hypertension. Methods to study retinal microvasculature may be even more sensitive.

Brain Health Vision Exams Training Summary:

Each RA completed a thorough training curriculum on operating the Zeiss IOL Master 500 and Zeiss OCT Cirrus 6000 equipment for the Brain Health Station. A summary of the major training stages are included below:

1. Complete Zeiss Academy online training curriculum for CIRRUS HD-OCT and IOL Master 500 equipment (3-5 hours). This is an online training platform that is self-paced and was completed before the RA came into the Research Center to use the equipment. Once completed, RA's are "certified" by Zeiss as having the basic skills necessary to operate the equipment.

2. Complete a half-day in-person training on Angiography 3x3 scan and OCT scan capturing with a certified trainer from Zeiss. These half-day trainings were split up into pairs so that each RA had ample practice time on the equipment, and also had the opportunity to experience the testing from the participant's perspective. The Zeiss certified trainer attended remotely over Zoom video due to the COVID-19 building restrictions.

3. Read and familiarize oneself with station's MOPs and protocols.

4. Additional training was completed remotely with Dr. Amir Kashani, Anoush Shahidzadeh and Elizabeth Corona (of Johns Hopkins & USC) on the specific image capture protocol utilized for the FHS Brain Health Station. This involved 3 consecutive weeks of 2-hour training/practice sessions. Dr. Kashani, Anoush Shahidzadeh and Elizabeth Corona offered guidance over Zoom while the RA's practiced capturing imaging on each other. Dr. Kashani offered tips on common technical challenges, how to troubleshoot poor image quality, the criteria for a successful image capture, and reviewed several of the images captured by the RA's to evaluate their quality.

5. Ongoing weekly meetings with Dr. Kashani, Dr. Seshadri, Anoush Shahidzadeh and Elizabeth Corona have occurred since the beginning of November 2020. These meetings allow for discussions on operational issues related to the Brain Health Station, but also troubleshooting of technical issues related to the examinations and further training, as needed. These meetings have served to augment the RA's training at the beginning of the station.

Brain Health Station Vision Equipment Summary:

The Brain Health Station's vision testing equipment includes the following:

1. Zeiss Cirrus 6000 HD-OCT: The Cirrus 6000 machine completes the Angiography and OCT scanning of the participants' eyes. Integrated into the machine is a PC with monitor, keyboard and wireless mouse.

2. Zeiss IOL Master 500: The IOL Master 500 measures the axial length of the participants' eyes. Included with the IOL Master 500 is a calibration kit that is used daily to calibrate the machine.

3. Power tables: Both the Zeiss machines come with powered tables. These tables allow the RA to raise or lower the table and equipment height to accommodate the participant's height by using a button on the table.

4. COVOC Blackout Curtains: Blackout curtains have been mounted on the exterior window in the exam room. These curtains ensure a dark testing environment to allow for pupil dilation. Generally, the curtains are always left down (closed) so the room remains dark.

5. Standing Lamp: A standing lamp is used to allow light in the exam room while the participant enters and sits in the chair. The lamp is situated next to the OCTA machine so that the RA can turn off the light without needing to walk to the doorway light switch.

6. Adjustable swivel chair for participant: Chair for participant allows them to adjust seat and armrest height, as well as to pivot easily from the OCTA machine, to the IOL Master machine, to the hearing tests (after the vision hearing).

7. Standard chair for RA to sit at while administering vision tests.

Obtaining OCTA Images

1. Turn on the device (Cirrus 6000 SD-OCTA) by pressing the power button.

2. The system will start up and the program should open on its own. However, if it does not, the program may be located on the desktop as icon "Cirrus HD-OCT."

3. After the program opens and the "Start Up Check" has finished, click "Continue".

4. For User Login, choose "Cirrus Operator" from the dropdown menu, type in the password, then click "Ok".

5. If registering a NEW patient, enter the patient information under the "Add New Patient" tab. After entering the information, click "Save" and then the "Acquire" button at the bottom-right side of the screen.
   OR
   If entering data on a returning patient, look up the patient by last name or ID on the "Find Existing" tab. Then the "Acquire" button at the bottom-right side of the screen.

6. For undilated patients, it is very important to eliminate ambient room lighting during imaging. This includes turning off room lights, closing black out curtains and closing the door to room. This will allow maximum pupillary dilation (mydriasis) for the imaging procedures below.

7. The protocol below should be performed on each eye separately starting with the right eye first, then the left as indicated below.

8. This protocol will use only one angiography option and one OCT option from the list.
   a. Perform "Angiography 3x3 mm" scan first. This is a 3x3 mm scan centered on the foveal avascular zone (the default will attempt to center the square over the foveal avascular zone when you click on the Angiography 3x3 mm option).
      - Prior to acquisition, make sure the foveal depression is actually centered for the two scans on the top-right corner of the screen (Figure 1).
        - If the foveal depression is not centered on the two scans in the top-right corner, you can move the box in the fundus image right, left, up, or down to adjust the foveal depression to the center (Figure 1).
        - The OCT scans denoted by the red arrows in Figure 1 should be in the top half of the boxes as seen in Figure 1.
      - Scans should be taken in quadruplicate (4 repeated scans). Have the subject blink three times between each acquisition.
      - Refer to Figures 1-4 for screenshots of the device for this scan sequence.
   b. The "Eye Tracking" feature must be active. This allows the device to track the eye movements of the patient in real time and avoid movement artifacts. If the outline of the box labeled "Capture" is green, the tracking feature is active. If it is red, the image cannot be tracked for one of several reasons.
      - In Figure 1, notice that the outline box around capture is green. This means the device is able to track.

- In Figure 2, notice the outline box around the capture is red. This means the device is not able to track.
    - If the “Capture” box is red, move the red circle with cross-hairs in the top-left panel to the center of the pupil by clicking on the center of the pupil.
    - Click on autofocus or manually focus using the arrows located underneath autofocus (Figure 2).
    - Make sure to ask the subject to blink their eyes a few times.
- In Figure 3, you will see the screen after you click “Acquire” in the bottom right.

9. After a single acquisition is complete, you will see four images (Figure 4): the front of the eye (pupil) in the upper-left, the OCT in the upper-right, the *en face* image on the bottom-left, and the angiogram on the bottom-right. Take note of the signal strength in the top-middle.
    a. The signal strength should be 7 or higher. If it is lower, the scan is not of sufficient quality and needs to be repeated. The fundus “signal strength” does not need to be 7 or higher. Simply ignore the fundus signal strength.
    b. The circle next to “tracked during scan” should be green.
    c. Please check the *en face* image in the bottom-left and angiogram in the bottom-right for any shadows that appear to obscure the underlying image or any dark regions that suggest an artifact such as movement or floater.
    d. If the scan appears poor for any reason (movement, floater, etc) click “Try Again” and try to capture the image again. If the image appears good, click “Save” and continue to the next scan.

10. Repeat step 6 and 7 a total of four times to obtain four repeated scans of the same region in the right eye.

11. Repeat all the above steps for the left eye.

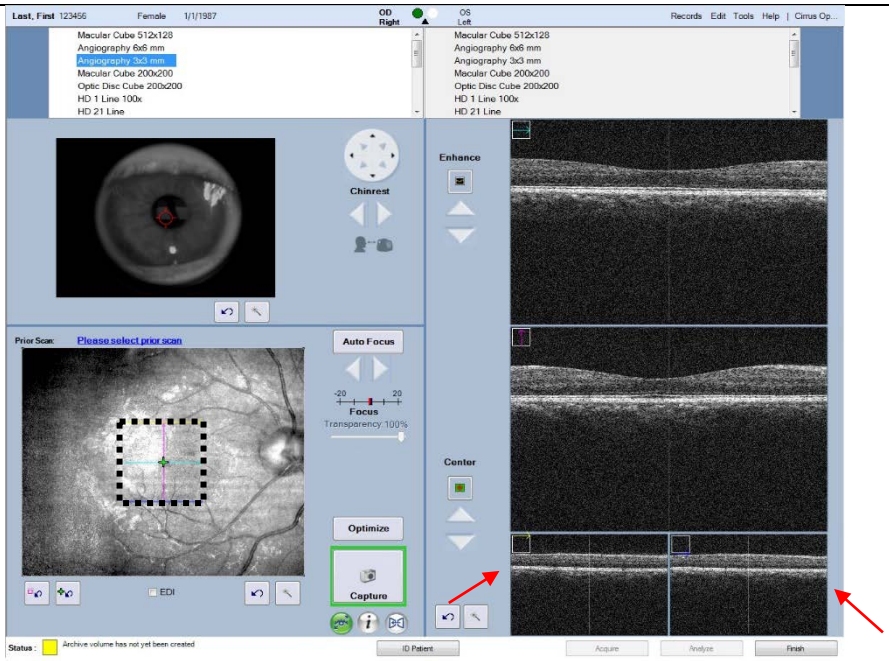


Figure 1: Screenshot of “Angiography 3x3mm” immediately prior to acquisition

Note:

The box around the “Capture” button should be green for successful acquisition.

The foveal depression should be centered on both the right-middle panels of the screen.

If the foveal depression is not centered in the middle of right-middle panels, the box with the dashed black outline can be moved to right, left, up, or down in order to center the foveal depression.

The red arrows point to the boxes where the OCT scans should be positioned in the top half of the box.

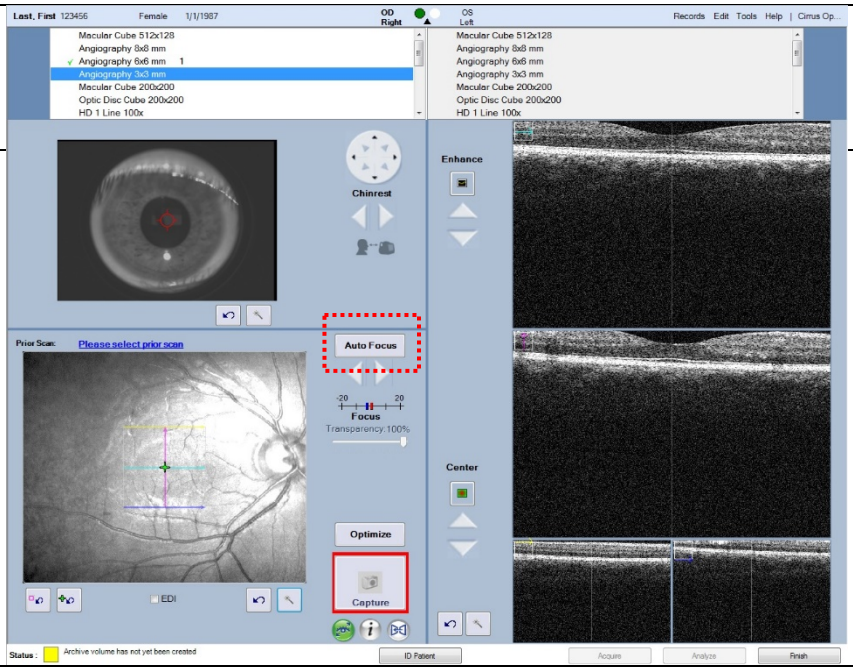


Figure 2: Screenshot of "Angiography 3x3mm" immediately prior to acquisition with red "Capture" box. In this case, the device cannot track because the OCT image is outside the acquisition window in the right panels. Autofocus option (red dotted box)

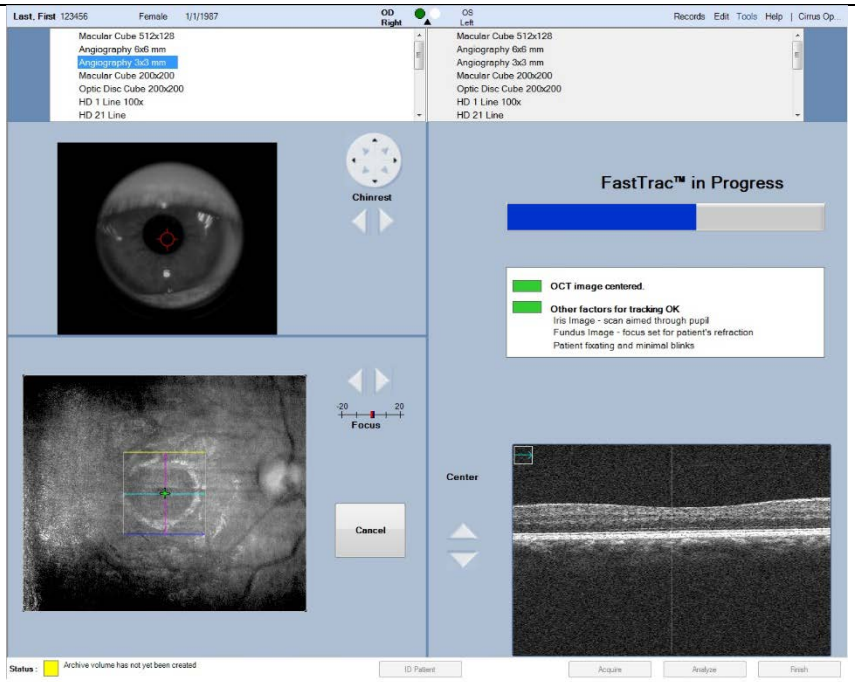


Figure 3: Screenshot of "Angiography 3x3mm" scan during scan acquisition

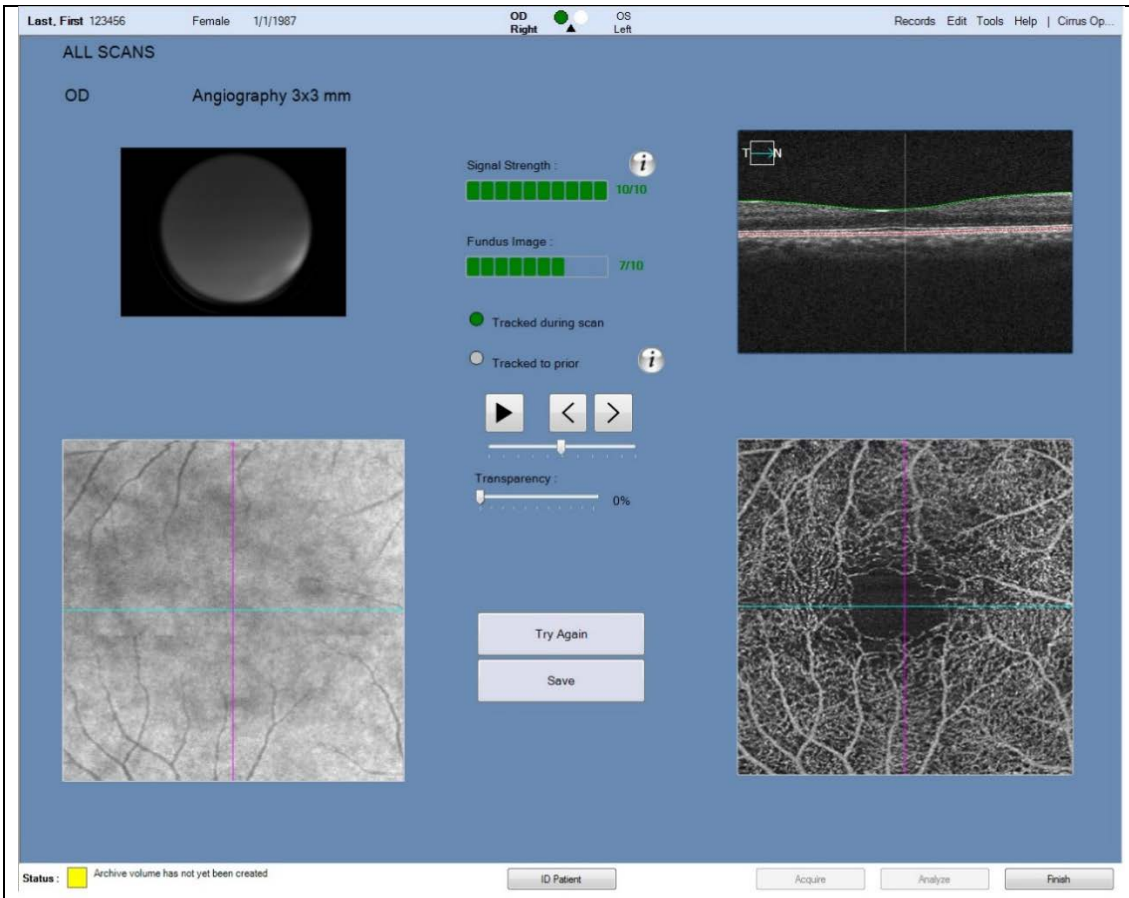


Figure 4: Screenshot of the "Angiography 3x3mm" scan after acquisition

12. Next start with the right eye and perform "Optic Disc Cube 200x200" scan. Click on "Optic Disc Cube 200x200." The default setting will move the fixation point so that the optic disc is centered on the scan pattern.
    - A box will appear in the lower-left panel with cross-hairs and two concentric circles in the middle.
    - Make sure the inner most circle is centered around the optic disc. The circle should be centered evenly on the disc (Figure 5).
    - Scans should be taken in quadruplicate (4 scans). Have the subject blink three times before the next acquisition.
    - Please note, the acquisition time for the Optic disc cube is much faster than that for the angiography scan.
    - Refer to Figures 5-8 for screenshot of the device for this scan sequence.

    As with the angiography scan, the "Eye Tracking" feature must be active. This allows the device to track the eye movements of the patient in real time and avoid movement artifacts. If the outline of the box labeled "Capture" is green, the tracking feature is active. If it is red, the image cannot be tracked for one of several reasons.

    - In Figure 5, you will notice that the outline box around capture is green. This means the device is able to track.

- In Figure 6, you will notice the outline box around the capture is red. This means the device is not able to track.
    - If the “Capture” box is red, move the red circle with cross-hairs in the top-left panel to the center of the pupil by clicking on the center of the pupil.
    - Make sure to ask the subject to blink their eyes a few times.
    - Click on autofocus or manually focus using the arrows located underneath autofocus (Figure 6).
    - If the “Capture box” is still outlined in red you may apply 1 drop of a commercially available artificial tear (Refresh™, Genteal™, Systane™, or Optive™) to each eye and try the scan again after 1 minute.
- In Figure 7, you will see the screen after you click acquire in the bottom-right.

13. After acquisition is complete, you will see five images: the front of the eye in the upper-left, the *en face* image on the bottom-left, and 3 OCT sections on the right side (Figure 8). Take note of the signal strength in the top middle.
    a. The signal strength should be 7 or higher. If it is lower, the scan is not of sufficient quality and needs to be repeated. The fundus “signal strength” does not need to be 7 or higher. Simply ignore the fundus signal strength.
    b. The circle next to “tracked during scan” will be green.
    c. Please check the *en face* image in the bottom-left for any shadows that appear to obscure the underlying image or any dark regions that suggest an artifact that disrupts the OCT scans.
    d. If the scan quality appears poor for any reason, click “Try Again” and try to capture the image again. If the image appears okay, click “Save” and continue to the next scan.

14. Repeat steps 9 and 10 a total of four times to obtain four repeated scans of the same region.

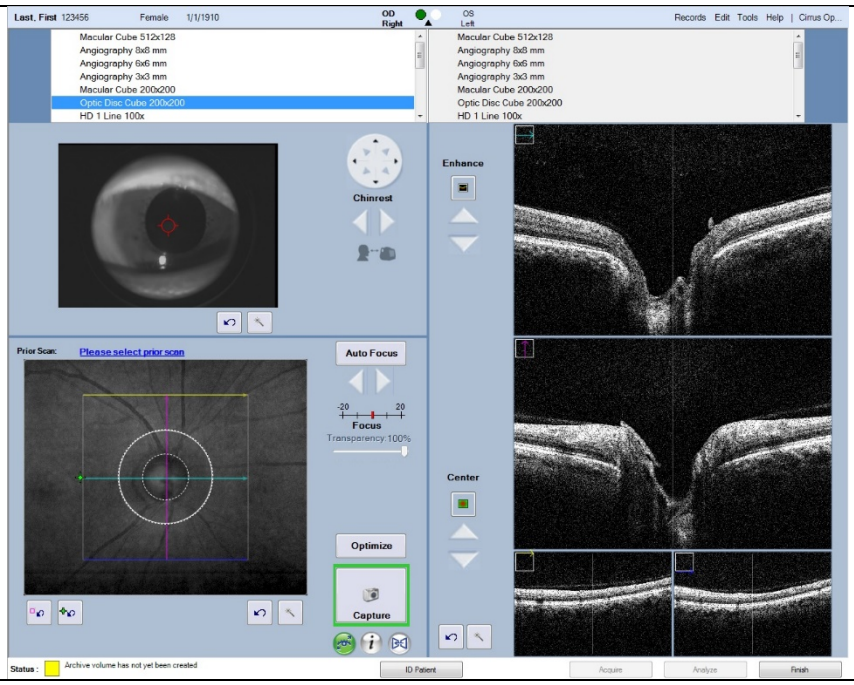


Figure 5: Screenshot of “Optic Disc Cube 200x200” immediately prior to acquisition

Note:

The box around the capture square should be green for successful acquisition.

The optic disc should be evenly centered within the smallest white circle in the lower-left panel.

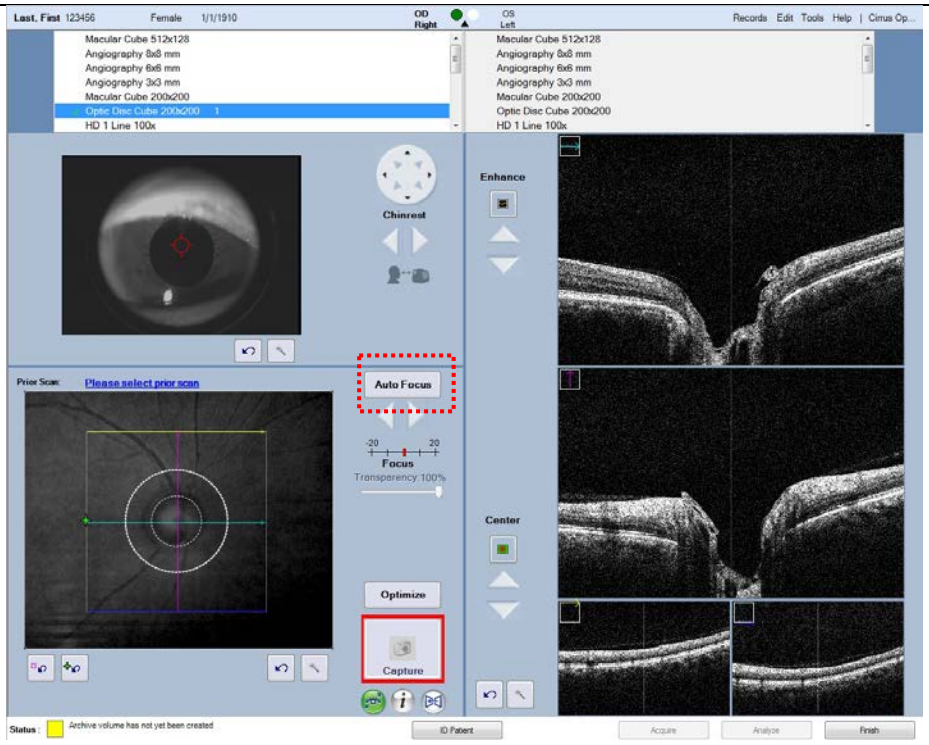


Figure 6: Screenshot of “Optic Disc Cube 200x200” immediately prior to acquisition with red “Capture” box. In this case, the red circle with cross-hairs should be re-centered in the top-left panel and the OCT image in the right panels should be kept completely inside the acquisition window. Autofocus option (red dotted box)

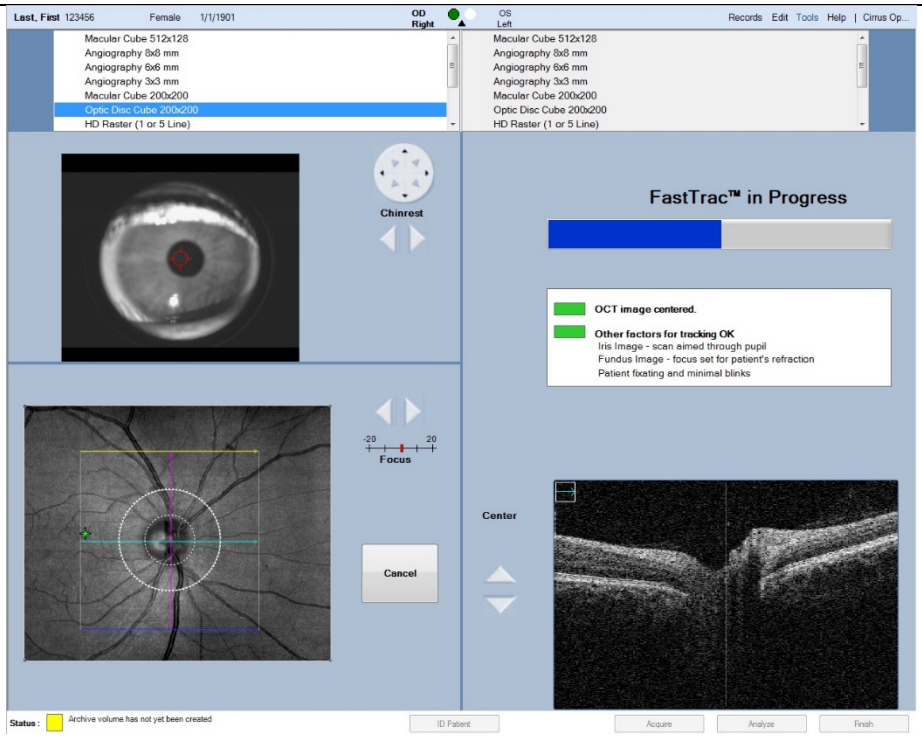


Figure 7: Screenshot of “Optic Disc Cube 200x200” scan during acquisition

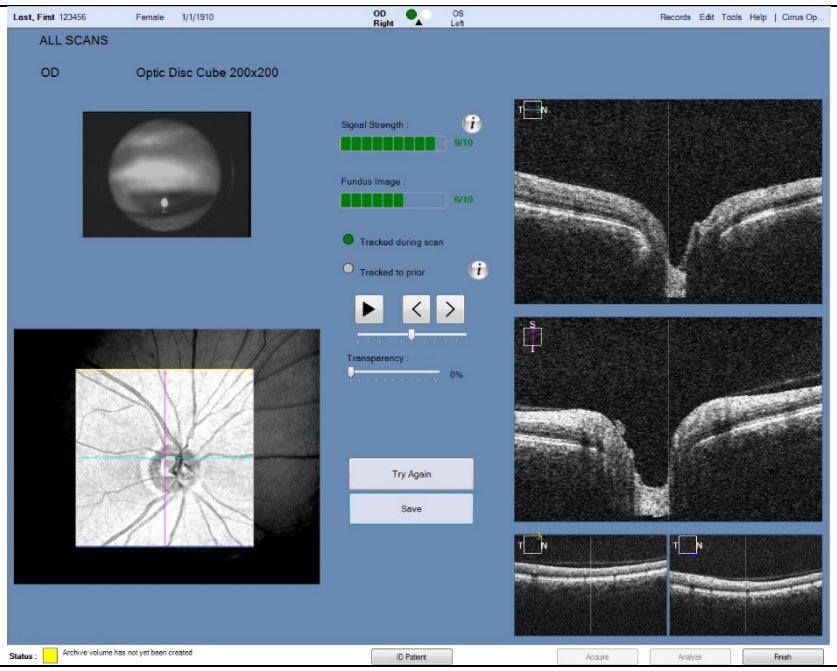


Figure 8: Screenshot of the “Optic Disc Cube 200x200” scan after acquisition

15. Perform steps 12-14 for the left eye.

16. After you save the last image, click “Finish” and review the images by clicking on the patients name in the “View Today’s Patient” tab or searching for the patient in “Find Existing Patient” tab and clicking “Analyze” at the bottom right-hand corner of the screen (Figure 9).
    a. Click on the "Angiography 3x3mm” and click “Angiography Analysis” on the upper right-hand side (Figure 10).
    b. The image will pop up in the center and the structural image will be on the right. Check the structural image for any artifacts that may results in any of the below artifacts (Figure 11-15).
    c. Check the image to ensure it is well centered in the acquisition window. Refer to centration guide for more information on how to do this.

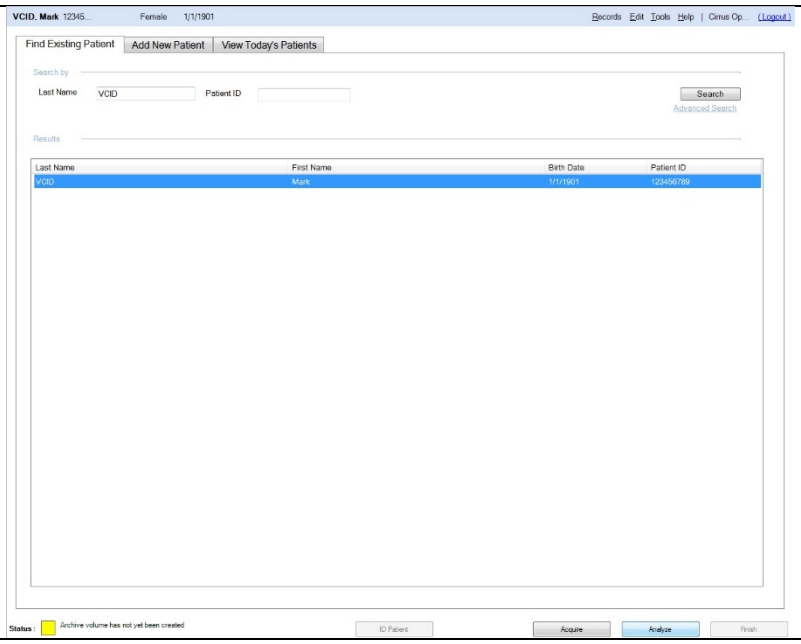


Figure 9: Screenshot of patient selection page image review

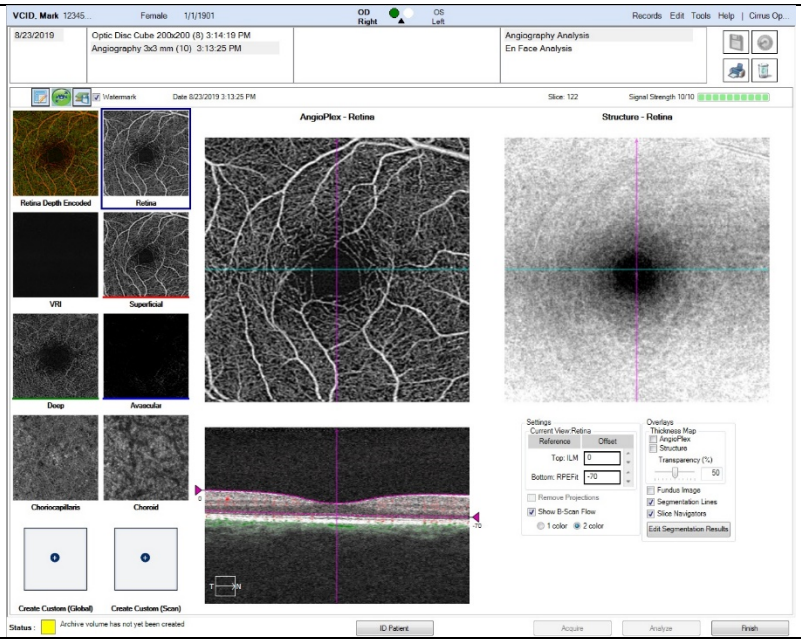


Figure 10: Screenshot of “Angiography Analysis” to review images.

17. Examples of good versus poor images are below for Angiography 3x3mm (Figure 16-20).

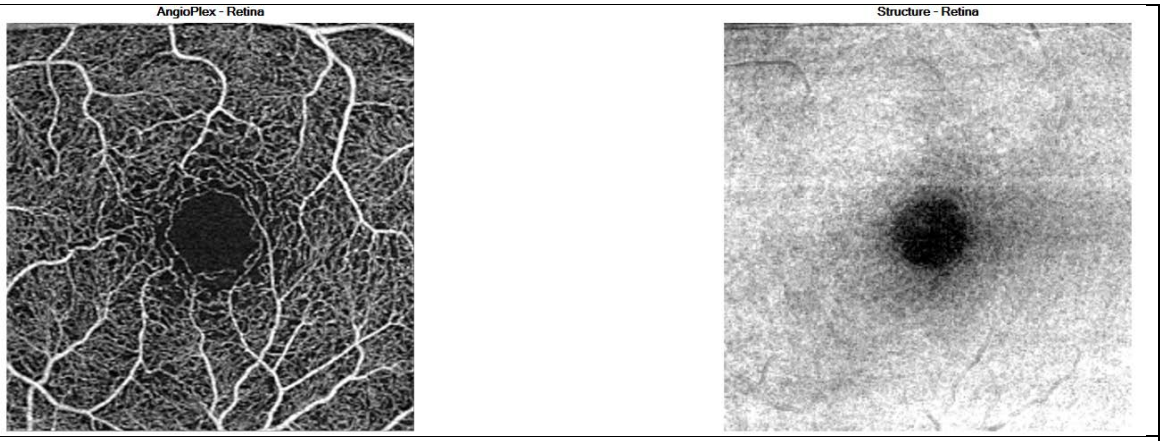


Figure 11: Examples of a “good” OCTA scan. The foveal avascular zone (dark region in the center) is well-centered. There are no bright or dark lines across either image. The larger vessels in the angiogram (left image) are not broken or discontinuous.

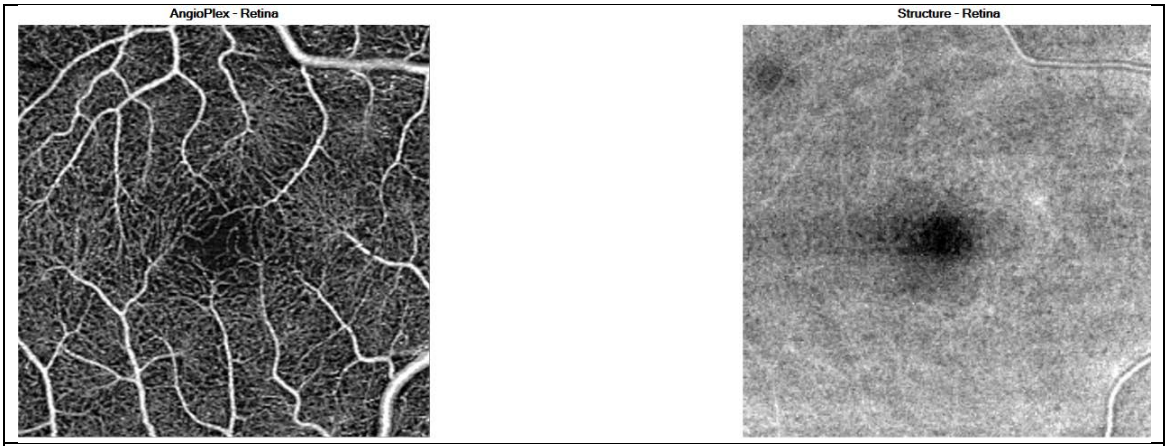


Figure 12: Examples of a “good” OCTA scan in subject with smaller foveal avascular zone. This subject has a relatively small foveal avascular zone but it is well centered in the image. There are no dark or bright lines across either image. There are no breaks or discontinuity in the larger vessels in the angiogram (left).

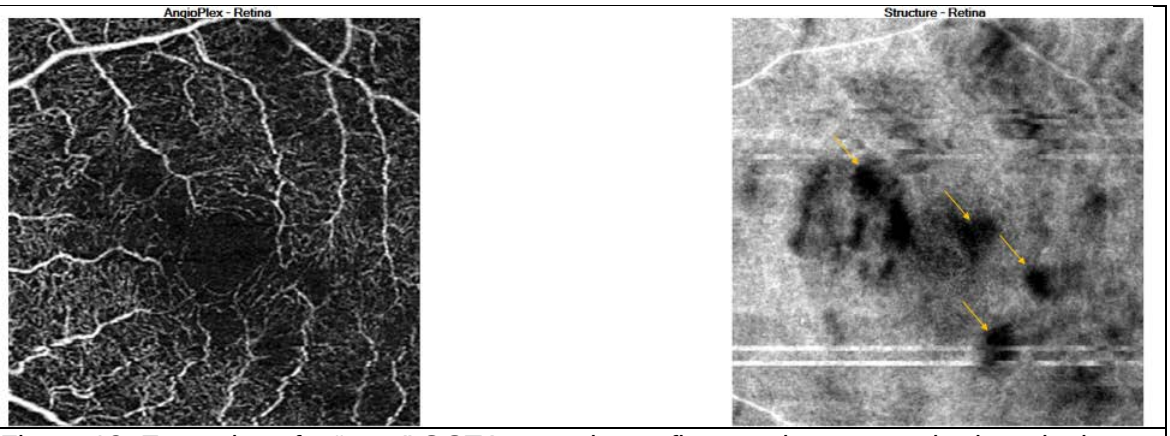


Figure 13: Examples of a “poor” OCTA scan due to floaters that cause shadows in the angiogram (left) and the structural image (right)

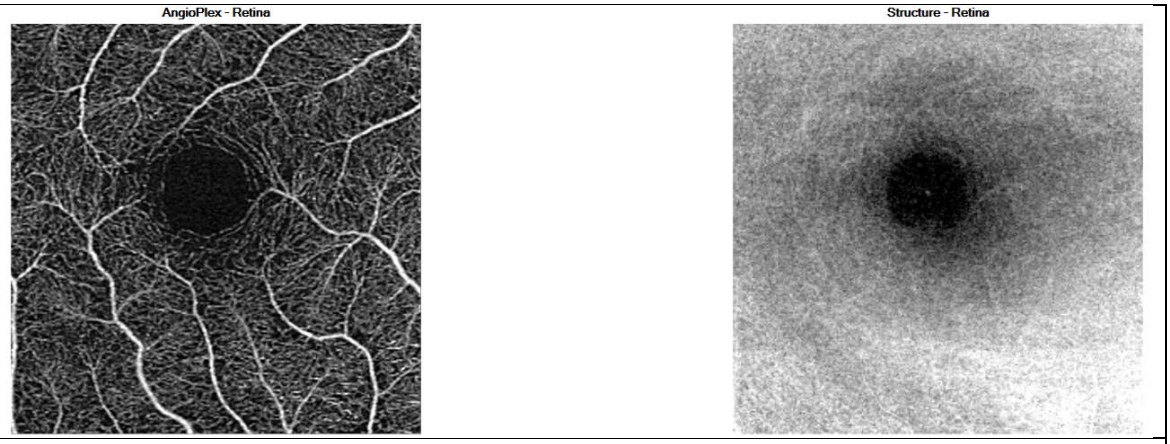


Figure 14: Examples of a “poor” OCTA scan due to decentered fovea

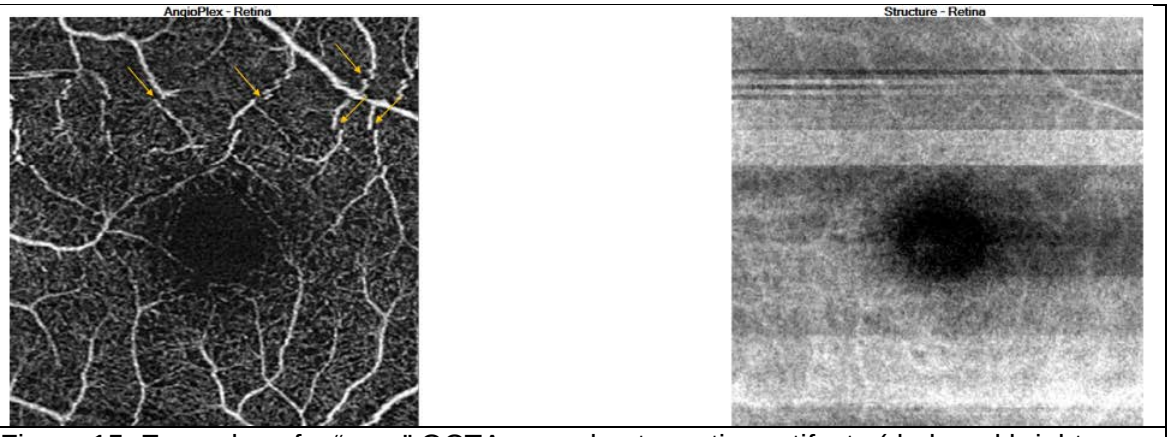


Figure 15: Examples of a “poor” OCTA scan due to motion artifacts (dark and bright bands across the structural image in the right panel). Also note the broken vessels (yellow arrows) in the angiogram on the left.

18. To view the optic disc cube images, click on “Optic Disc Cube 200x200” (Figure 16).
    a. Once you click on it, there will be a list of option to choose from on the upper right corner. Choose “En Face Analysis” (Figure 16).
    b. The image will show the fundus image of the optic disc cube along with a blue line to scroll through the associated OCT (Figure 17).
    c. With your cursor, click on the blue line to scroll through the scan to ensure that no part of the OCT scan occurs outside the box.
    d. Check the image to ensure it is well centered in the acquisition window. Refer to centration guide for more information on how to do this.

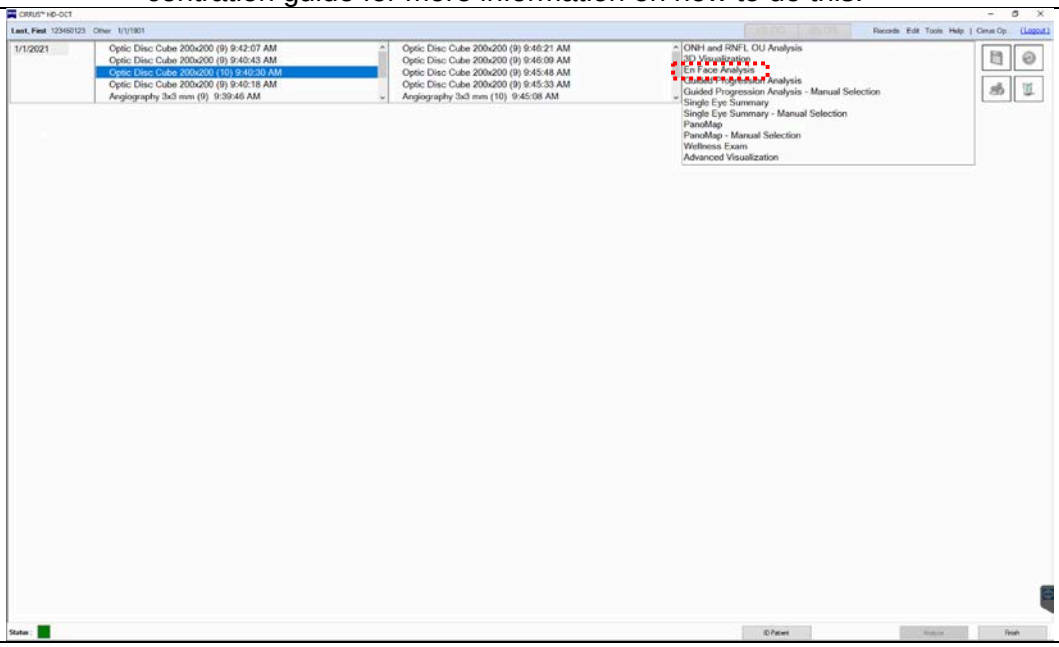


Figure 16: Screenshot of “Optic Disc Cube 200x200” to review images. Select En Face Analysis show in red-dotted circle.

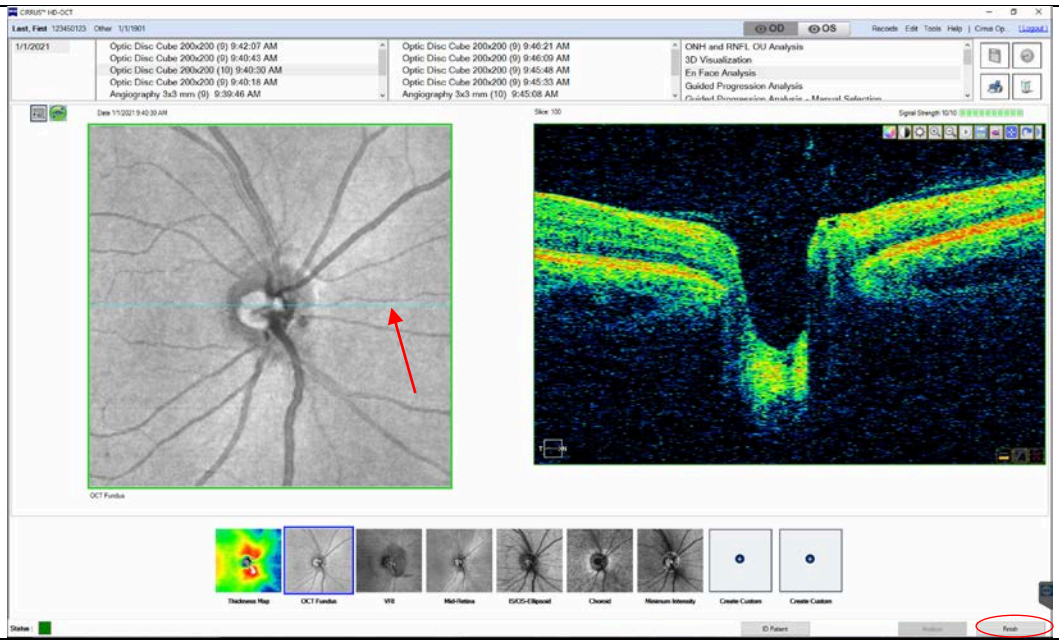


Figure 17: Screenshot of “En Face Analysis” to review images. Blue horizontal line noted with red arrow to scroll through associated OCT image. Red circle around “Finish” button.

19. After you are done reviewing the images, click “Finish” at the bottom right corner (Figure 17).

Export Deidentified OCTA Data

1. In the software, click on “Records” in the top right-hand corner (Figure 18).

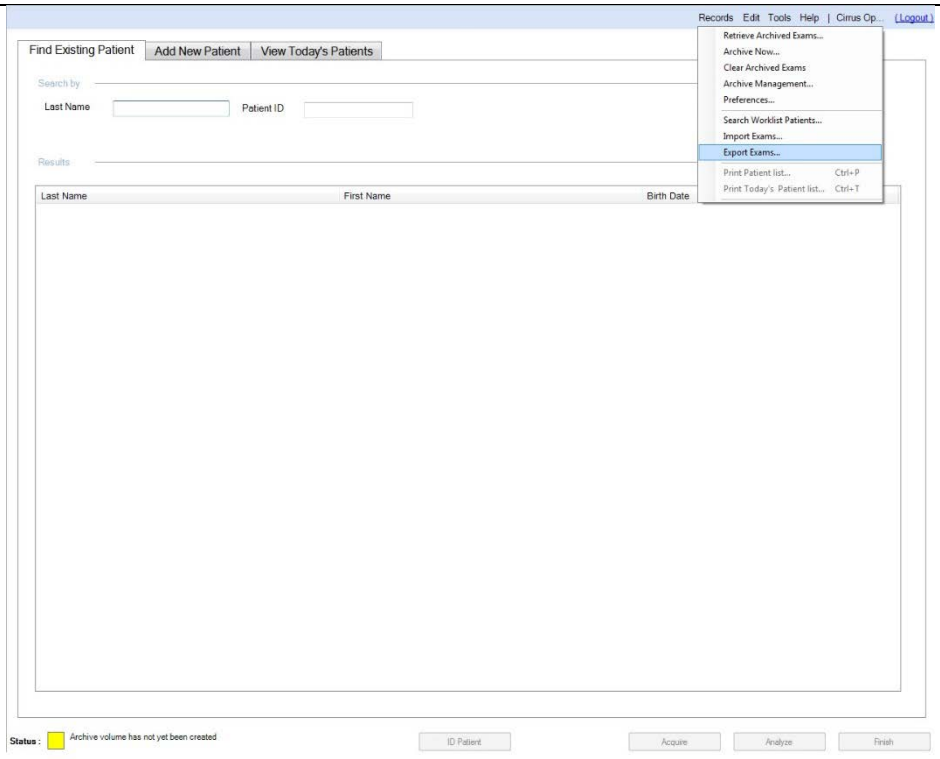


Figure 18. Screenshot of records to export exams

2. Choose “Export Exams…” and a dialog box comes up (Figure 19).

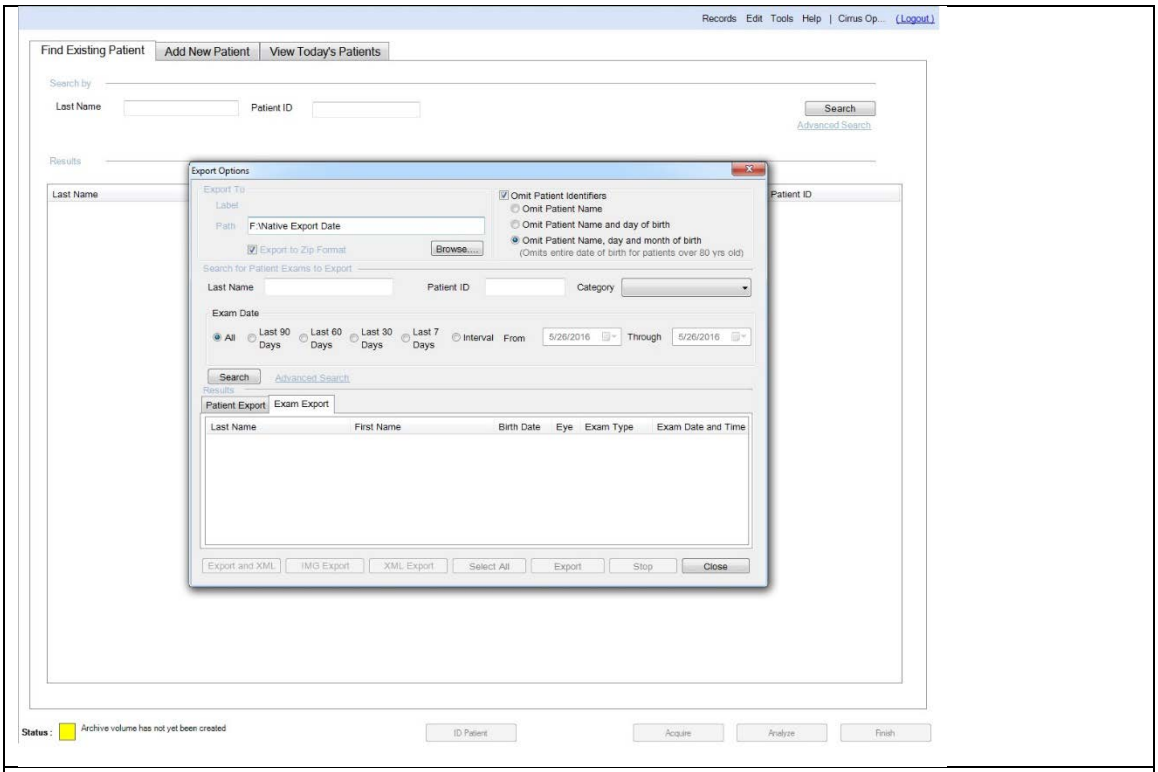


Figure 19: Screenshot of Export Options for deidentified export

3. Choose the path to export to and uncheck “Export in Zip Format”.

4. The checkbox next to “Omit Patient Identifiers” should remain unchecked.

5. You can search by last name, Patient ID, or choose “All”, “Last 90 Days”, “Last 60 Days”, “Last 30 Days”, “Last 7 Days” or an interval. It would be best to export data patient-by-patient so they can be easily identified.

6. After choosing the first patient, click “Search”.

7. The names and ID of the patient appears.

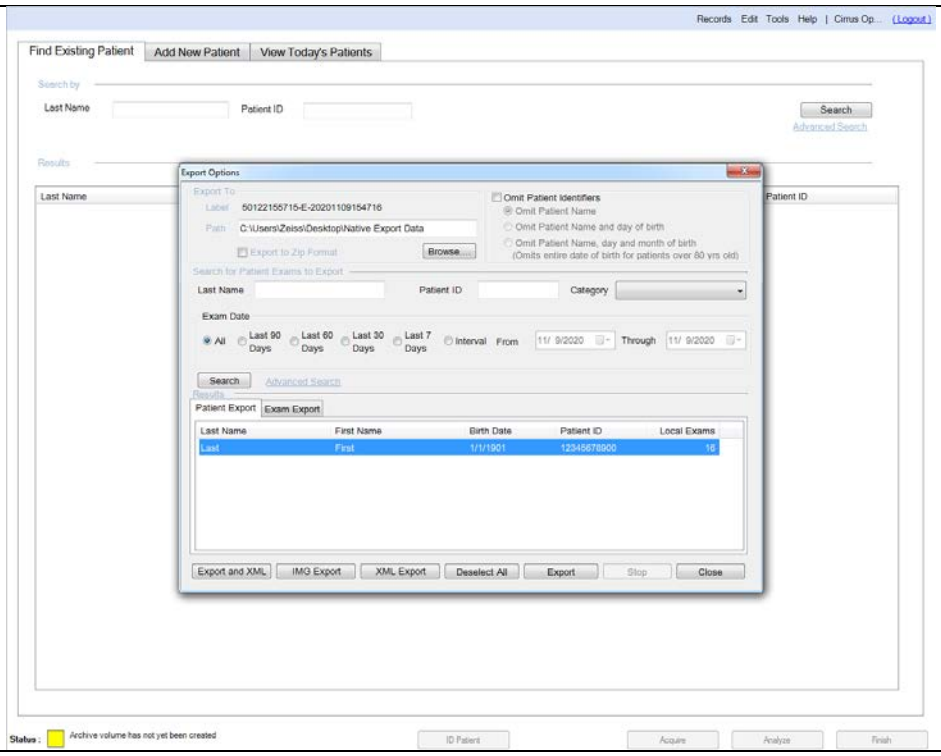


Figure 20: Screenshot of patient selection

8. Click on the patient you would like to export (Figure 20).

9. Click on the “Exam Export” tab and to choose which exam(s) to export (Figure 21). All exams should be exported.

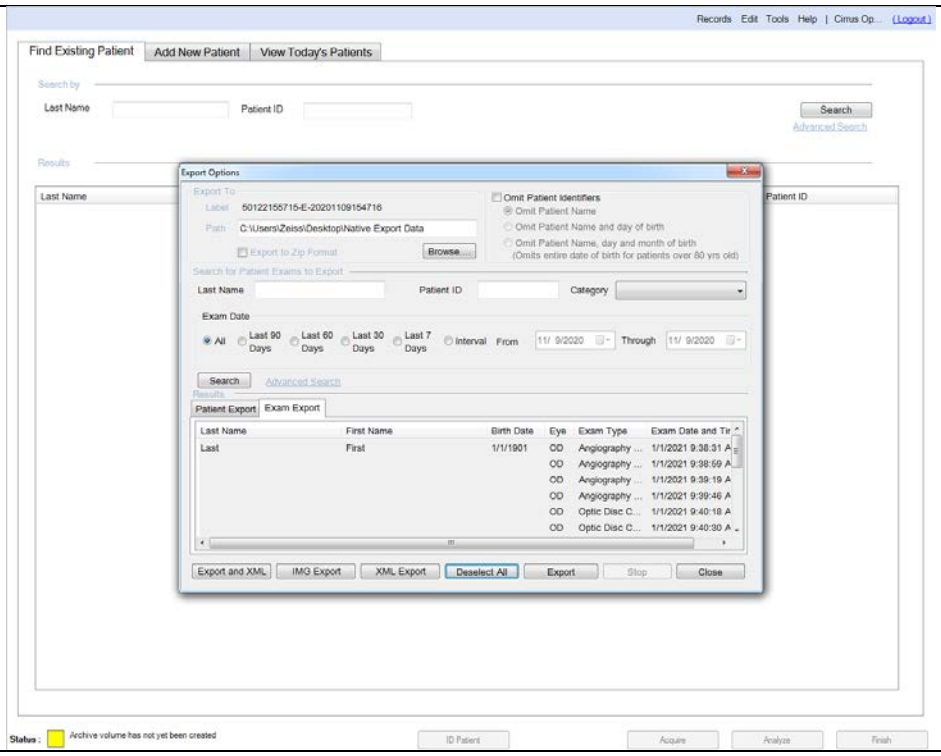


Figure 21: Screenshot of the exam selection page

10. Then click “Export.”

11. After the export is completed, proceed to export the next patient by following the instructions above.

IOL Master Measurements

1. Turn on the device by pressing the switch on the right side of the device (Figure 1).

Figure 1: Picture of power button on right side of the device

2. When it prompts you to check the calibration of your device, click “Start Test” if it is the first time using the device for that day (Figure 2). The device needs to be calibrated daily.

Figure 2: Start up screen when device is turned on and asks for calibration

3. To test the calibration, you need a test eye (Figure 3). Adjust the device using the joystick (Figure 4) to align the pupil and then press the button when the traffic light icon turns green (Figure 5). This must be done twice (once per eye) so the test eye will need to be moved to the left after the right eye is completed.

Figure 3: Test eye used for calibration

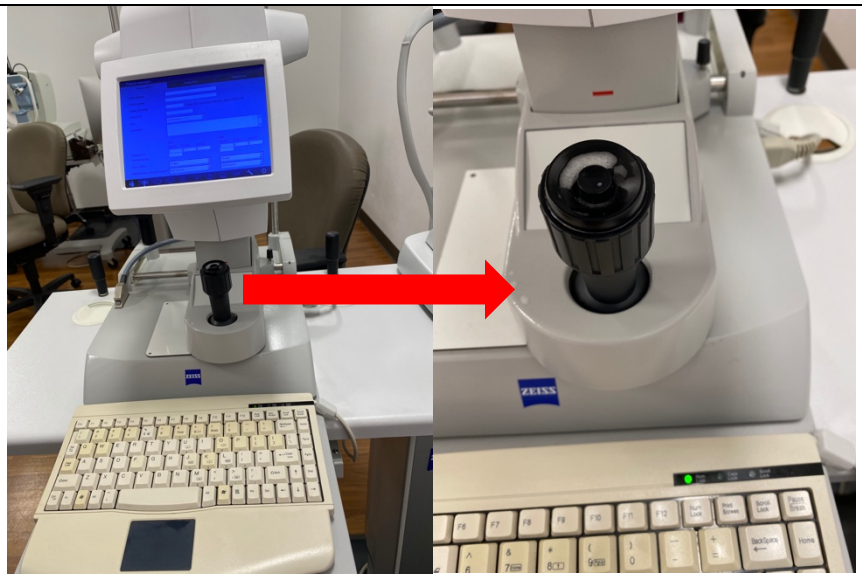


Figure 4: Joystick to move in, out, and side to side of device
Notes: Red arrow points to magnified version of joystick on device

Figure 5: Calibration screen with green traffic light in red-dashed circle

4. After calibration is complete, click on the “New Patient” icon on the bottom left corner of the screen (Figure 6).

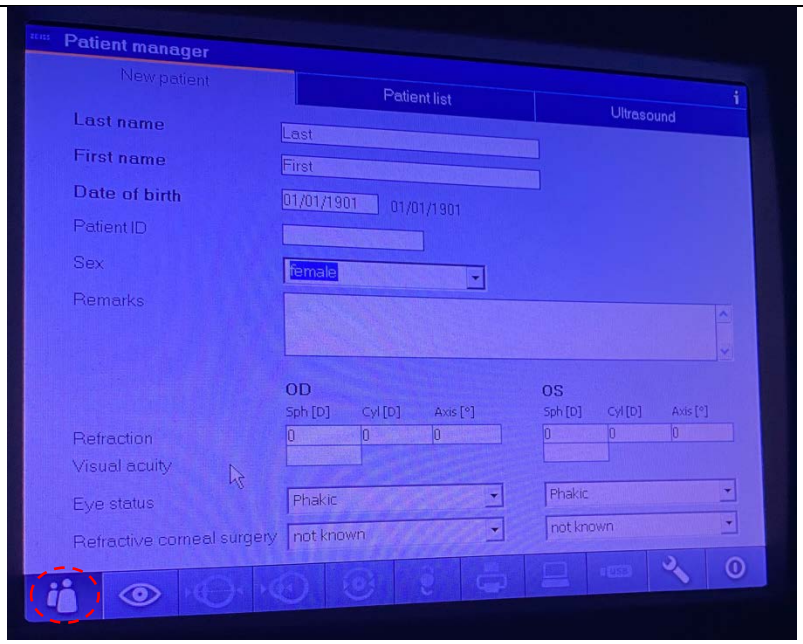


Figure 6: “New Patient” tab in red-dashed circle

5. Under the tab “New Patient,” enter the participants name, date of birth, and ID.
6. After entering the participant’s information, click on the “Eye” icon on the bottom of the screen next to the “New Patient” icon (Figure 7).

Figure 7: “Eye” icon screen in red-dashed circle

7. It will take you to a screen where you can start acquiring the measurements (Figure 7).
8. With the joystick, align the camera with the pupil until the traffic light turns green (Figure 8) then click the button on the joystick to capture (Figure 4).

Figure 8: Traffic light is green

9. Repeat step #8 for the other eye.
10. Make sure to record the measurements given on the device.
11. After you have completed, you can click the “New Patient” icon to acquire the next patient by repeating steps #4-10.

Image Review and Patient Notification Protocol

1. Anoush and Dr. Kashani will review OCTA images, axial lengths and corneal curvatures of subjects and make designations of potential incidental findings.

2. Each subject will be designated as "normal," "abnormal" or "urgent." These designations will be made on the master FHS study excel spreadsheet maintained by FHS (Tim and Hongshan) as a shared, secure, online document with study team. These designations have the following meaning:

    a. “Normal” – The study results are unremarkable for the subject’s age. Subject should continue with standard of care evaluations or initiate standard of care evaluations with PCP or eye care provider per AAO guidelines.

    b. “Abnormal” – One or more of the study results appear abnormal but are of uncertain clinical significance. Subject should review the study results with PCP or eye care provider at regularly scheduled evaluations. If subject does not have PCP or eye care provider, they should obtain one for further evaluation.

    c. “Urgent” – One or more of the study results appear abnormal and may pose a significant risk to the subject’s health. Review of the findings and further assessment by a licensed physician is recommended urgently (within 1 month or sooner).

3. For subjects designated as “abnormal” or “urgent” Tim will generate a letter from the FHS template letters and send to Dr. Sobrin via Datamotion.

4. If needed, Tim and Dr. Sobrin will clarify findings with the JHMI/USC Team. For subjects with “urgent” findings a phone call to the subject may be made by Dr. Sobrin or FHS staff. Telephone calls to subjects will be documented on telephone tracking form by Dr. Sobrin with date/time, content of conversation with participant and their PCP, and actionable items.

5. For subjects designated as “normal,” FHS (Tim) will send "normal" letters to FHS Core Exam Administrator (Barbara Inglese), who will send out normal letters with the regular Core Exam mailing. Copies of the normal letters will be placed in FHS chart by FHS Core Exam Administrator.

6. For subjects designated as “abnormal” or “urgent”, Tim will send these finalized letters (after review and approval by Dr. Sobrin) to FHS Core Exam Administrator (Barbara Inglese), who will send out letters with the regular Core Exam mailings. Copies of the “abnormal” or “urgent” letters, along with any telephone tracking forms completed by Dr. Sobrin, will be placed in the FHS chart by FHS Core Administrator.

7. Tim will send all "PCP" letters to FHS Core Exam Administrator, who will send out letters to all providers, and will file a copy of the PCP letters into the participant’s FHS chart

8. Tim will document all phone calls by Dr. Sobrin to a participant and/or their PCP in the PTS Call Log.

9. “Abnormal” and “urgent” letters/cases will be reviewed on the last Wednesday meeting of each month with the team.

Quality Control

Quality control checks will be completed monthly by the Brain Health Station PI’s and staff. This will include a monthly check for imaging and data completeness, to be completed by FHS Data Management staff, the Research Technician from USC/JHMI, and FHS Brain Health Station Program Manager and RA’s.

We will compare data received through the OCTA machine/IOL Master and listed on a master spreadsheet, and will compare this against participant schedules for the FHS Core Exam through RedCap. All missing images will be reconciled by the RA’s staffing the station each week, in collaboration with the Program Manager and Data Manager. Furthermore, the quality of OCTA imaging and IOL Master measurements are reviewed by Dr. Kashani, Dr. Seshadri, Anoush Shahidzadeh and Elizabeth Corona monthly. Feedback is then provided to the FHS Brain Health Station RA’s bi-monthly at standing meetings to help improve their skills and ability to capture high quality imaging.

The Framingham Heart Study
A Project of the National Heart, Lung, and Blood Institute and Boston University

[Participant Address]

Dear [Participant Name]:

Thank you for your participation in the Brain Health Study, an ancillary study of the Framingham Heart Study. Your involvement in this study provides us with very important information to better understand how your eyes, hearing and walking can reflect the health of the brain. We hope you found it to be an interesting experience.

I am writing this letter as a summary of the results of your participation in the eye exam component. During your visit we performed optical coherence tomography angiography (OCTA) examinations, axial length and corneal curvature measurements of your eyes. The results of these test appear unremarkable. However, please note that these results are not intended for clinical use and do not replace evaluation and testing that is recommended by your licensed eye care provider or primary care physician. We recommend that you continue care with a licensed eye care provider. If you do not have a licensed eye care provider, we encourage you to contact your primary care physician for further advice about standard-of-care evaluations that may be appropriate for you.

The website for the American Academy of Ophthalmology is also provided below for your reference and additional information about eye care and resources that you may find useful.

American Academy of Ophthalmology Website for Public and Patients: https://www.aao.org/eye-health

If you have any questions, please don't hesitate to call us. Please feel free to call [redacted]

Thank you again for your continued support of the Framingham Heart Study.

Sincerely,

[redacted]

73 Mt. Wayte Avenue • Framingham, MA 01702 • 508.872.6562 tel • 508.626.1262 fax

The Framingham Heart Study
A Project of the National Heart, Lung, and Blood Institute and Boston University

Participant Address]

Dear [Participant Name]:

Thank you for your participation in the Brain Health Study, an ancillary study of the Framingham Heart Study. Your involvement in this study provides us with very important information to better understand how your eyes, hearing and walking can reflect the health of the brain. We hope you found it to be an interesting experience.

I am writing this letter as a summary of the results of your participation in the eye exam component. During your visit we performed optical coherence tomography angiography (OCTA) examinations, axial length and corneal curvature measurements of your eyes. Please note that these results are not intended for clinical use but may be useful for your primary care doctor or eye care provider. Please review the findings with them for further information. Your doctor will carefully consider whether these findings need to be followed up with additional tests or treatments, based on a consideration of your entire medical history and further examination. These tests showed the following findings of uncertain clinical significance:

Include abnormal findings here.

As mentioned above, these findings require review by a licensed eye care provider. If you do not have a licensed eye care provider, we encourage you to contact your primary care physician. The website for the American Academy of Ophthalmology is also provided below for your reference and additional information about eye care and resources that you may find useful.

American Academy of Ophthalmology Website for Public and Patients: https://www.aao.org/eye-health

If you have any questions, please don't hesitate to call us. Please feel free to call T[redacted]

Thank you again for your continued support of the Framingham Heart Study.

Sincerely,

Lucia Sobrin, MD
Ophthalmologist

73 Mt. Wayte Avenue • Framingham, MA 01702 • 508.872.6562 tel • 508.626.1262 fax

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[Participant Address]

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I am writing this letter as a summary of the results of your participation in the eye exam component. During your visit we performed optical coherence tomography angiography (OCTA) examinations, axial length and corneal curvature measurements of your eyes. Please note that these results are not intended for clinical use but may be useful for your primary care doctor or eye care provider. Please review the findings with them for further information. Your doctor will carefully consider whether these findings need to be followed up with additional tests or treatments, based on a consideration of your entire medical history and further examination. These tests showed the following findings:

Include abnormal findings here.

These findings appear abnormal and require urgent review by a licensed eye care provider for confirmation. If you do not have a licensed eye care provider, we encourage you to contact your primary care physician. The website for the American Academy of Ophthalmology is also provided below for your reference and additional information about eye care and resources that you may find useful.

American Academy of Ophthalmology Website for Public and Patients: https://www.aao.org/eye-health

If you have any questions, please don't hesitate to call us. Please feel free to call [redacted]

[redacted] again for your continued support of the Framingham Heart Study.

Sincerely,

Lucia Sobrin, MD
Ophthalmologist

73 Mt. Wayte Avenue • Framingham, MA 01702 • 508.872.6562 tel • 508.626.1262 fax

The Framingham Heart Study
A Project of the National Heart, Lung, and Blood Institute and Boston University

Participant Address]

Dear Dr. [PCP Name]:

Your patient, [Participant Name], has participated in an ancillary research study of the Framingham Heart Study. Their involvement in this research study provides us with very important information to better understand how eyes, hearing and walking can reflect the health of the brain.

I am writing this letter as a summary of the research results of their participation in the eye exam component. Please note that these results are not intended for clinical use but we are providing them as a source of information for you to review in case you find any of the information useful. We have encouraged your patient to discuss these results with you and have also provided a copy of the results to the patient.

During the visit we performed optical coherence tomography angiography (OCTA) examinations, axial length and corneal curvature measurements. These scans showed the following findings:

Include abnormal findings here.

If you have any questions, please don't hesitate to call us. Please feel free to call [redacted]

[redacted] again for your continued support of the Framingham Heart Study.

Sincerely,

[redacted]

73 Mt. Wayte Avenue • Framingham, MA 01702 • 508.872.6562 tel • 508.626.1262 fax

OCTA SCREENING WORKSHEET			
Date of OCTA Screening: ___ ___ / ___ ___ / ___ ___ ___ ___ (MM/DD/YYYY)			
Questions	**No**	**Yes**	**N/A**
1. Have you ever been diagnosed with any of the following eye diseases?			
1.1. Glaucoma	☐	☐	
1.2. Diabetic Retinopathy	☐	☐	
1.3. Dry Age-Related Macular Degeneration	☐	☐	
1.4. Wet Age-Related Macular Degeneration	☐	☐	
1.5. Retinal Vein Occlusion (stroke of the eye)	☐	☐	
2. Have you ever had any of the following procedures done?			
2.1. Cataract Surgery in the right eye	☐	☐	
2.2. Cataract Surgery in the left eye	☐	☐	
2.3. Laser Surgery on either eye for any reason *(excluding cosmetic or refractive procedures such as LASIK or cataract surgery)*	☐	☐	
2.4. Injections into or around either eye *(excluding cosmetic procedures)*	☐	☐	
3. Do you take any prescription eye drops (excluding artificial tears)?	☐	☐	

Anterior Segment Scan Analysis

To analyze or print an anterior segment scan, click **Analyze** from the ID PATIENT screen. See Access Analysis on page 4-1 and Image Display Options During Analysis on page 4-12 for more information about the ANALYSIS screen and selecting an analysis.

Central Corneal Thickness Measurements for Anterior Segment Cube 512x128, and Anterior 5 Line Raster Scans

Note: The measurement tool  for Anterior Segment Cube 512x128 and Anterior 5 Line Raster scan analysis is calibrated to measure corneal tissue only. It is not calibrated for other materials such as air, other types of tissue, implants, or contact lenses. If the caliper tool is used for measuring other materials, measurement results may be inaccurate.

Note: Anterior Segment 512x128 and Anterior Segment 5 Line Raster scans are not corrected to account for beam scanning geometry, the optics of the CIRRUS system, or refraction at the anterior and posterior surfaces. Therefore, the measurement tool only measures vertical distances.

Note: Measurements of a patient's corneal thickness using the measurement tool must be interpreted by qualified health care professionals in the context of the entire clinical assessment of the patient.

Corneal Measurements for Anterior Chamber, Wide Angle to Angle, HD Cornea, HD Angle, and Pachymetry scans

Note: The measurement tools for Anterior Chamber, Wide Angle to Angle, HD Cornea, HD Angle, and Pachymetry scan analysis are calibrated to measure corneal tissue and anterior segment structures below the cornea based on the refractive index of the corneal tissue only. The tools are not calibrated for other materials such as air, other types of tissue, implants, or contact lenses. If the measurement tools are used for measuring other materials, measurement results may be inaccurate.

Note: In cases with corneal implants, keratoplasty, or other conditions that may introduce abrupt changes in corneal contour, pachymetry results may not be valid and should be assessed in the context of the patient's medical history together with other diagnostic information.

Note: Anterior Chamber, Wide Angle to Angle, HD Cornea, HD Angle, and Pachymetry scans are corrected to account for beam scanning geometry, and refraction on the corneal surfaces. Therefore, the measurement tools can measure vertical, horizontal, and diagonal distances.

Note: Measurements of corneal tissue and anterior segment structures using the measurement tool must be interpreted by qualified health care professionals in the context of the entire clinical assessment of the patient.

Analyze Screen Image Controls for Anterior Segment Scans

Anterior Segment Cube 512x128 and Anterior 5 Line Raster Scans

Menu image control options are available by right clicking the mouse on an OCT B-Scan. See Image Display Options During Analysis on page 4-12.

To sequence through slices of an Anterior Segment Cube 512x128 scan or the scan lines of an Anterior Segment 5 Line scan, do any of the following:

- For Anterior Segment Cube 512x128 scans, use the slice navigators of the cube displayed in the area under the iris image.

  or

  For Anterior Segment 5 Line scans, click one of the scan lines displayed on the iris image or one of the thumbnail images.
- Click an OCT B-Scan image and use the mouse scroll wheel.
- In full screen mode, use the scroll bar at the right side of the image or the mouse scroll wheel.

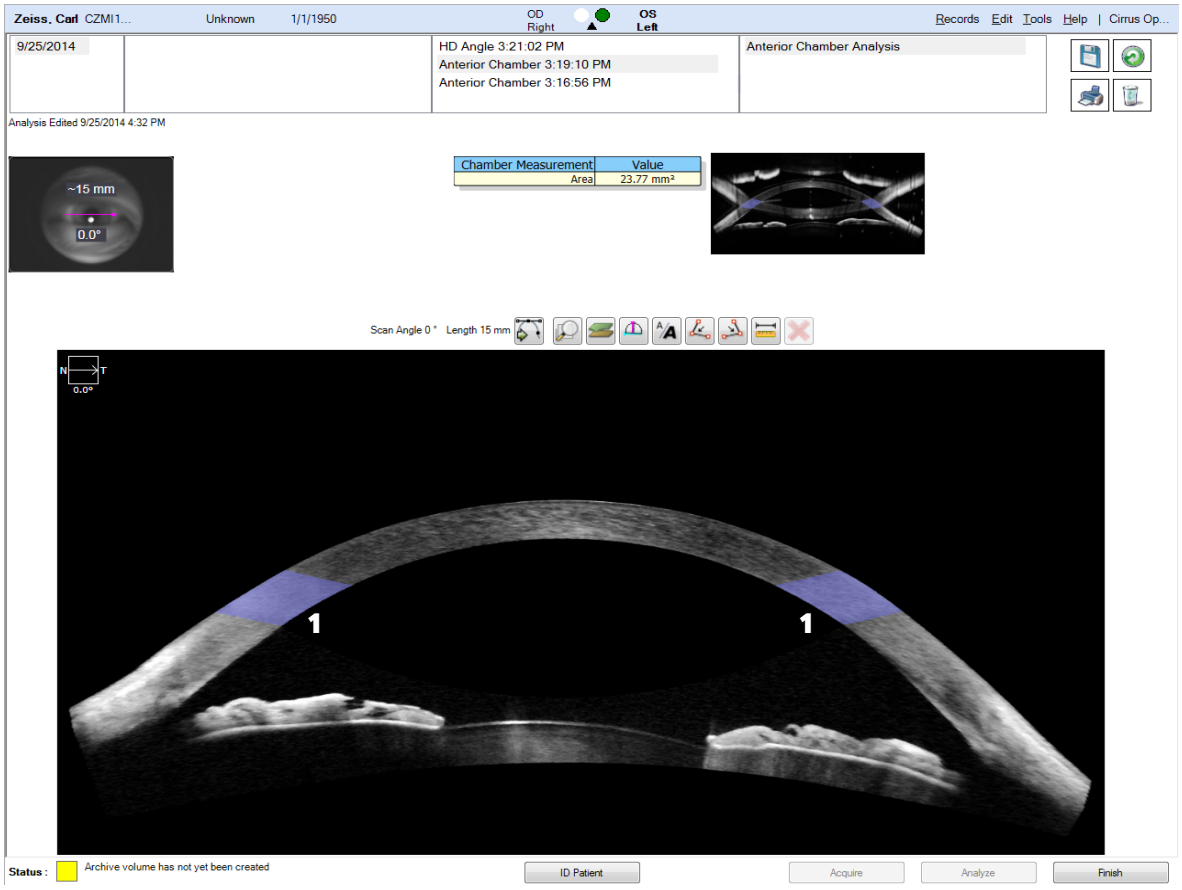
Anterior Chamber, HD Angle, HD Cornea, Wide Angle to Angle Scans

The following image buttons are available when the mouse pointer is on an OCT B-Scan.

-  Color/Grayscale/Reverse grayscale: Click to switch the image display between color, grayscale, and reverse grayscale.
-  Adjust brightness/contrast: Click to put the image in interactive brightness/contrast mode. To adjust contrast, drag the pointer horizontally over the image. To adjust image brightness, drag the pointer vertically.
-  Zoom: Click to zoom on the image and then click and drag the mouse to pan to an area of interest.
-  Reset Zoom: Click to reset the zoom.
-  Save Image: Saves the current image on screen in the location and type of format you select.
-  Reset: Click to reset the image display to its default settings.

Anterior Chamber Scan Analysis

The Anterior Chamber Analysis is the only analysis available for the Anterior Chamber scan. When you select an Anterior Chamber scan from the ANALYZE screen scan list, the Anterior Chamber Analysis for that scan is automatically displayed.



1 Mirror artifact

Figure 6-11: Analysis Screen, Anterior Chamber

The Anterior Chamber screen shows the iris image with the single line scan pattern used to generate the displayed Anterior Chamber scan. The length and angle of the scan are indicated on the iris image and also are displayed above the OCT B-Scan. A chart indicating the Chamber Area Measurement and the Value (mm^2) is displayed to the right of the iris image. A small image of the mirrored corneal image that is not processed is also displayed.

Note: The Anterior Chamber scan is acquired using a full axial field of view that displays an image composed of both the true image data and a mirror artifact that is poorly resolved and inverted in the axial direction. It is possible to hide the mirror artifact in most parts of the image, but the mirror artifact data intersects the true data at two places in the cornea. These intersections appear as distinctive bars on the image. If you need to see these parts of the cornea, use the HD Cornea scan.

Anterior Chamber Analysis Image Tools

The following image tools are available on the Anterior Chamber Analysis screen:

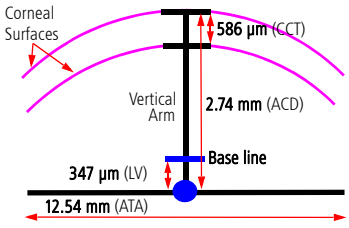
- **Toggle Processed/Raw Image**: Click to switch between a processed view of the OCT image that is corrected for optical distortion and the default raw image view.

- **Toggle Opacity**: Click to show/hide the mirror images.
- **Show/Hide Layers**: Click to show/hide the overlay lines denoting the anterior cornea (green line), the posterior cornea (red line), and the residual stromal line (RSL) (magenta line).
- **Add ACD Tool:** Click to automatically place the ACD (anterior chamber depth) tool. See Anterior Chamber Depth (ACD) Tool below for more information.
- **Add Annotation Tool**: Use this tool to save comments on the OCT image. Click the **Add Annotation Tool** button, move the mouse to where you want the annotation text, and click to place it. Enter text in the **Enter annotation text here** field. To insert a new line, press the **Enter** key on the keyboard, and then click **OK**. You can move the text by clicking and dragging it. Check **show arrow** to show an arrow from the text to an area of interest. You can move and resize the arrow by clicking and dragging the arrow tip. Double-click to edit the text. You can enter up to 64 characters, including spaces.
- **Add Left Angle Tool**: (see "Add Angle Tool" on page 6-21): Use this tool to measure an angle of interest for the left side of the corneal image. Click and then drag the tool to place it on the angle and then click and drag the endpoints to measure the angle.
- **Add Right Angle Tool** (see "Add Angle Tool" on page 6-21): This tool functions the same as the Left Angle Tool, but is used for the right side of the corneal image.
- **Add Caliper**: Use this tool to measure distances of interest. Click the button to automatically place it in the center of the image. Move the mouse pointer to the tool until it changes to ( ), and then click and drag the tool to place it. Move the mouse pointer to an end line until the end line turns yellow, and then click and drag it to the desired length and angle of rotation.
- **Delete**: This button is available when a measurement tool is placed on the image. Select the tool you want to delete, and then click the button.

Anterior Chamber Depth (ACD) Tool

The Anterior Chamber Depth (ACD) Tool is designed primarily for the routine measurement of four things: corneal thickness (CT), angle to angle distance (ATA), anterior chamber depth (ACD), and lens vault (LV). However, the tool does allow you to vary from this routine and place the arms and endpoints independently.

To take measurements with the Add ACD tool



1. Click the **Add ACD Tool button** to place the tool on the image (see drawing on left as well as Figure 6-12). The top end of the vertical arm is automatically positioned at the anterior surface of the cornea, and another marker is positioned at the corneal vertex of the posterior surface to measure the corneal thickness (CCT). You can adjust the position of the vertical arm by clicking and dragging it horizontally.
2. Click and drag to place the right and left endpoints in each angle to measure the angle to angle distance (ATA).

3. Click and drag to place the base line to the anterior surface of the crystalline lens to measure anterior chamber depth (ACD) and the lens vault (LV). To measure ACD in eyes with aphakia or pseudophakia, drag the base line to the pupillary plane.

   The measurements will appear on the OCT image and a summary of the measurements will appear in a table above the OCT image. Figure 6-12 below shows the ACD Tool placed correctly at the angles and the anterior surface of the lens.

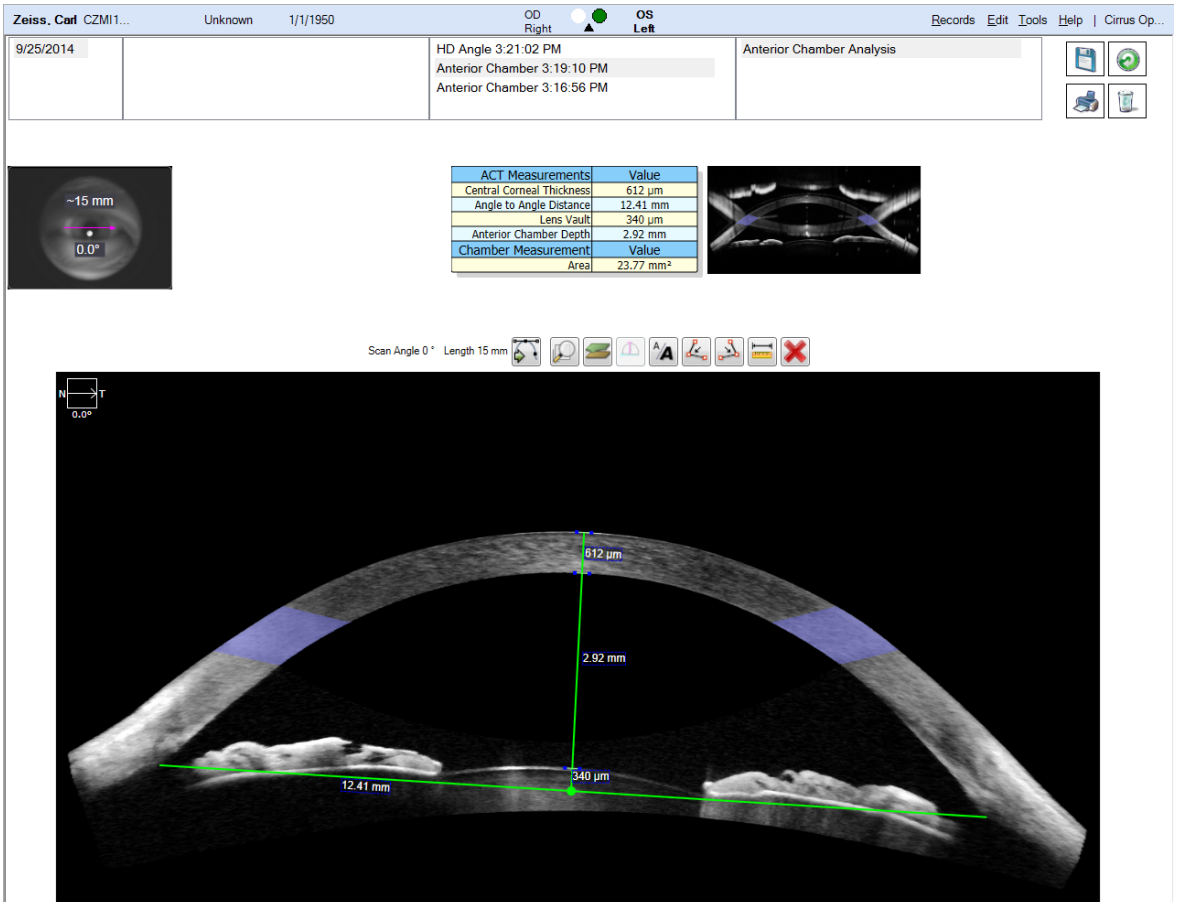


Figure 6-12: ACD Tool Placed Correctly on a Anterior Chamber Scan

Add Angle Tool

1. Place point A of the Angle Tool at the scleral spur.
2. Adjust point B to touch the corneal endothelium.
3. Adjust point C to touch the iris. See Figure 6-13.

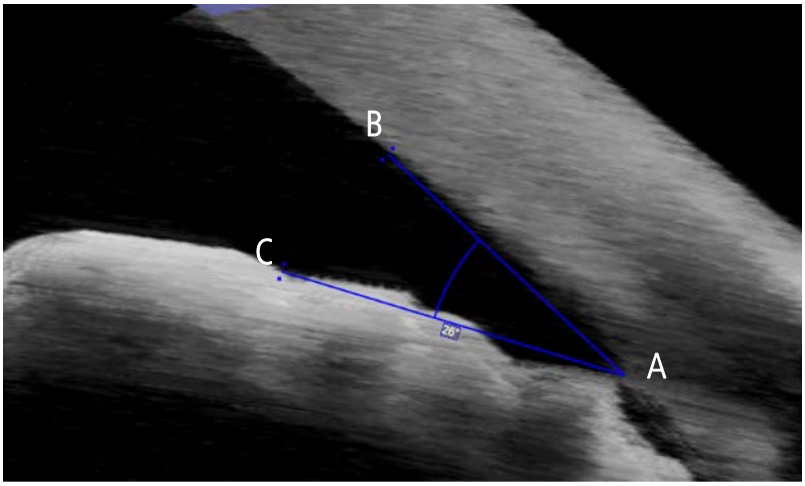


Figure 6-13: How to apply the Add Angle Tool

Note: The anterior chamber angle images and analyses provided by CIRRUS HD-OCT are not intended as substitutes for gonioscopy.

Anterior Segment Cube 512x128 Analysis

Anterior Segment Analysis and 3D Visualization are available for the Anterior Segment Cube 512x128 scan. See Chapter 7, Analyze Scans: 3D Visualization, for more information on 3D Visualization.

The Anterior Segment Analysis screen (Figure 6-14) for the Anterior Segment Cube 512x128 scan displays the iris viewport with the scan area and scan navigators superimposed. The X slice (fast - B-Scan) is shown in the upper OCT viewport and the Y slice (slow - B-Scan) is shown below it. Click and drag the slice navigators in the iris viewport to move through the slices.

Figure 6-14 shows an Anterior Segment Analysis of the cornea thickness.

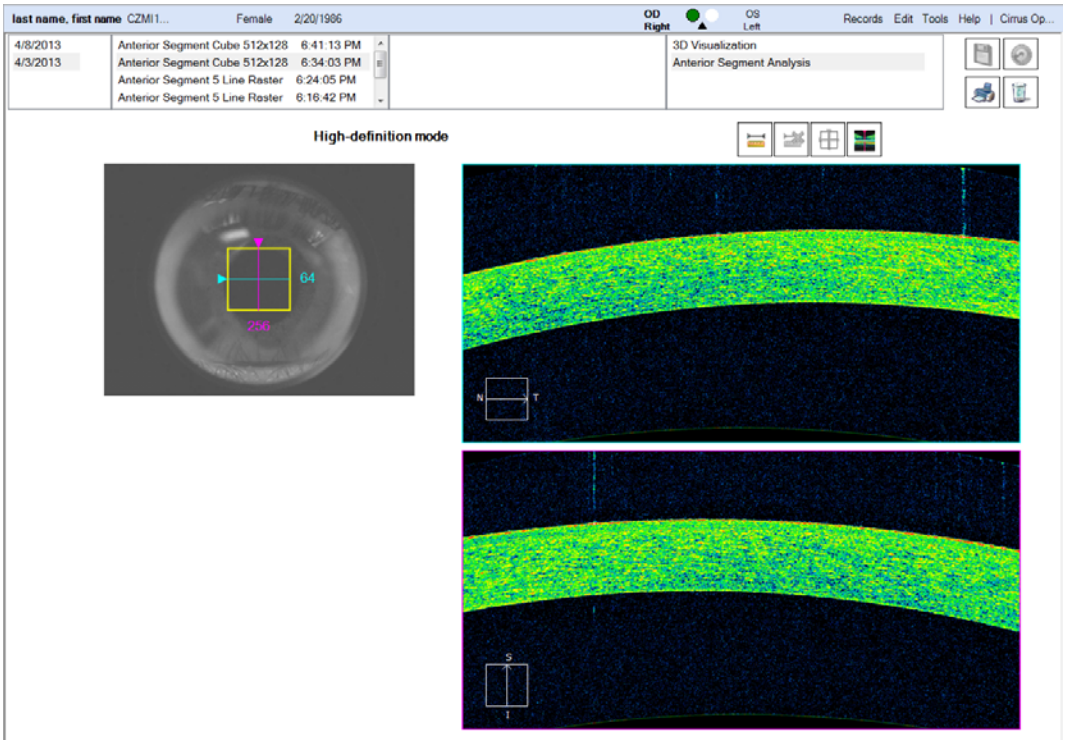


Figure 6-14: Anterior Segment Analysis – Cornea Thickness

Figure 6-15 shows an Anterior Segment Analysis of the iris/cornea angle in High-definition mode.

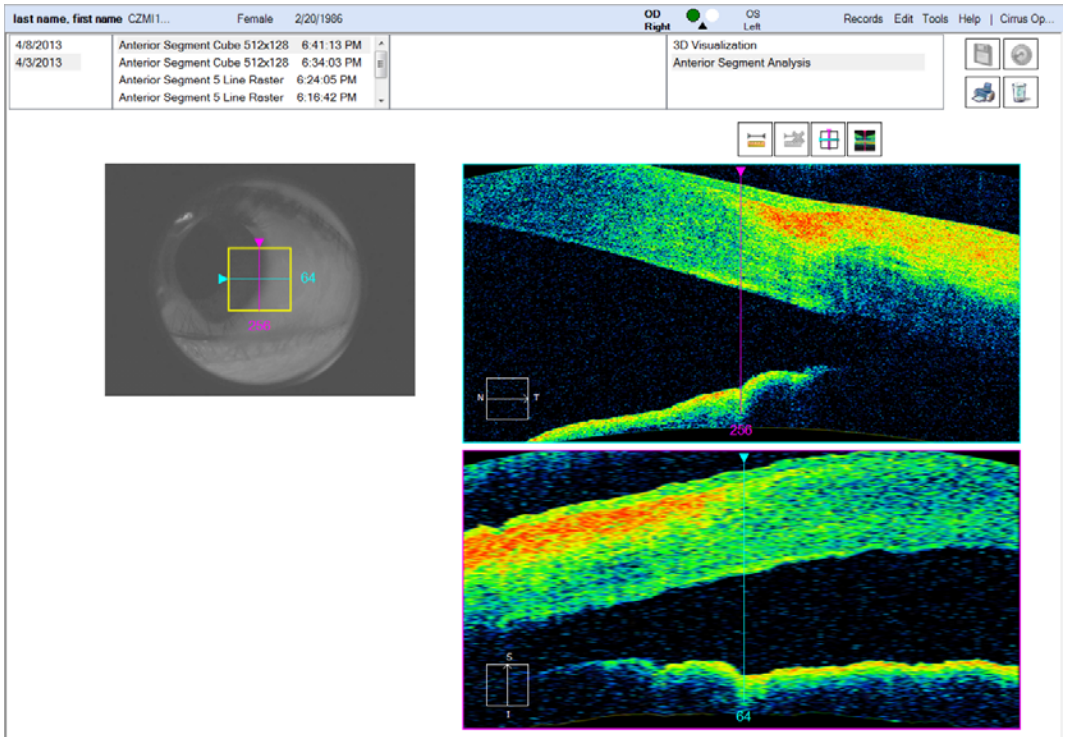


Figure 6-15: Anterior Segment Analysis – Iris/Cornea Angle (High-Definition Mode)

Anterior Segment Analysis Image Tools for Anterior Segment Cube 512x128 Scans

The Anterior Segment Analysis has the following image tools:

 Measurement ruler to measure central corneal thickness

 Delete button to delete selected measurement lines

 Snap button to reset scan navigator lines to center

 Show/hide high resolution images button

Central Corneal Thickness (CCT) Measurement

The operator is advised to evaluate the scanned image prior to making CCT measurements. The corneal image should have well-defined posterior and anterior surfaces, should not have excessive motion artifacts and corneal reflections on the central cornea, especially within the area where the measurement caliper is to be placed.

Note: CCT measurements may be easier to obtain on HD Cornea or Anterior Chamber scans.

The following conditions may affect the ability to obtain a good corneal image for CCT measurements:

1. Inability of the patient to maintain fixation, including patients with poor visual acuity.
2. Excessive corneal reflection resulting from certain intraocular lenses, corneal abrasions and corneal opacities.
3. Presence of contact lenses. The junction of some contact lenses and the corneal surface may not be easy to visualize. Patients should remove contact lenses prior to scanning for a CCT measurement.

Central corneal measurements should be made at the apex of the cornea. To determine the apical area:

1. Estimate where the center of the pupil is on the image and move the scan navigators so that they intersect at that point.
2. Click the ruler button, and align the ruler vertically against the magenta slice navigator on the horizontal scan.
3. The center of the cornea can be identified by moving the scan navigators throughout the entire scan volume and noting how the scans appear to move up and down within the box. The apical area, being closest to the instrument lens, will have the highest scans. By using the ruler as a reference point while moving the slice navigators, find the highest horizontal and vertical scans.
4. The CCT measurement should be made at the intersection of the highest horizontal and vertical scans, using the ruler on the horizontal scan. The intersection of the scans is identified by the position of the mauve slice navigator. Adjust the position of the ruler and place the white horizontal lines of the ruler ends on the anterior and posterior surfaces of the cornea. The measurement is in micrometers. See Figure 6-16 for the correct position of the ruler and the proper placement of the calipers.

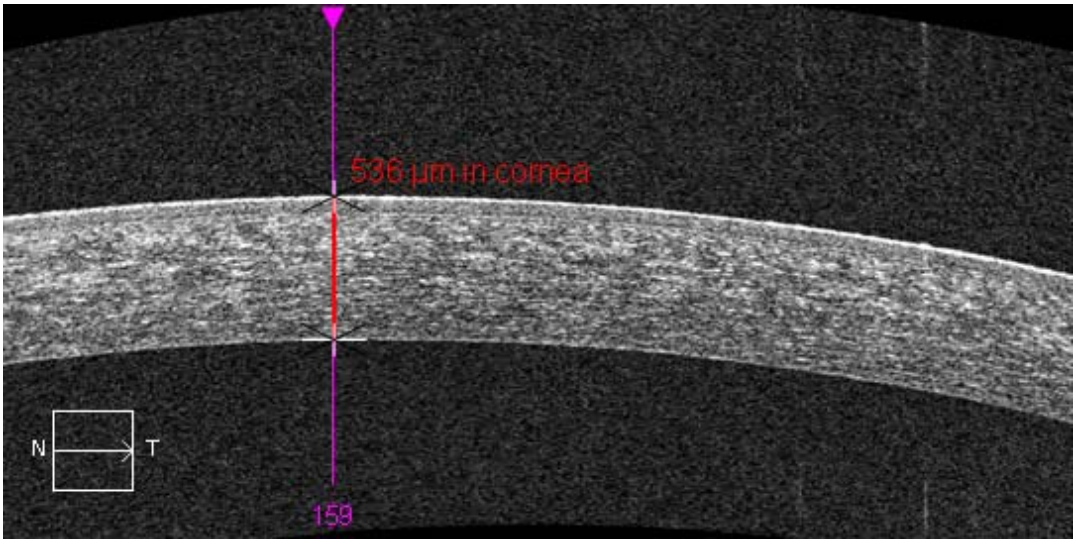


Figure 6-16: Positioning the Ruler

Note: Vertical distances on the tomogram reliably show tissue thickness and tissue refractive index. Horizontal distances cannot be measured quantitatively on these tomograms. When applied to Anterior Segment scans, the Ruler measures only vertical distances, with the scale factor set appropriately for measurements within the cornea.

Note: The Ruler is calibrated for measuring corneal tissue only, based on the refractive index of the cornea. It is not calibrated for other tissue types.

Note: The Anterior Scan Cube 512x128 is initially be displayed in the High-definition mode. Click the **Show/hide high-resolution images** button to allow scrolling through the cube images or move a slice navigator to a different slice.

Note: For the Anterior Segment 5 Line Raster scan, only the ruler buttons are available.

Anterior Segment 5 Line Raster High Definition Images Analysis

The High Definition Images analysis is the only analysis available for the Anterior Segment 5 Line Raster scan. When you select an Anterior Segment 5 Line Raster scan from the ANALYZE screen scan list, the High Definition Images analysis for that scan is automatically displayed.

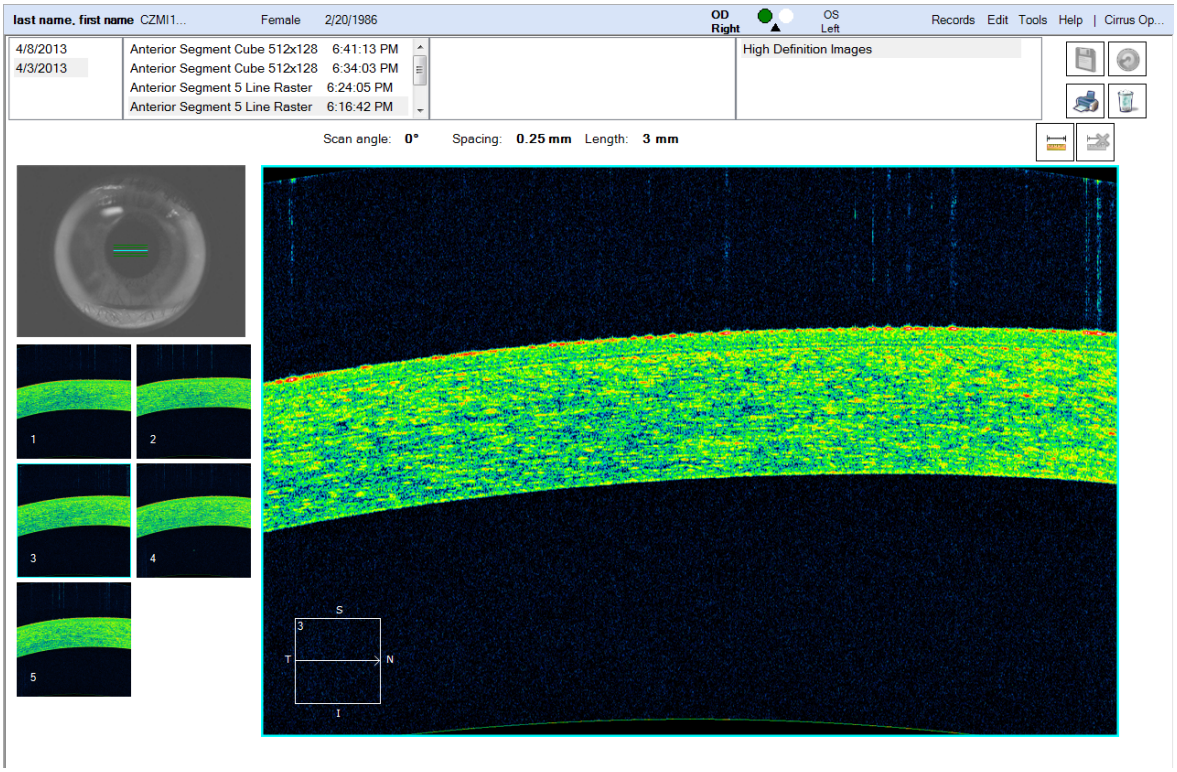


Figure 6-17: High Definition Images Analysis – Cornea Thickness

The High Definition Images analysis screen displays the iris viewport with the scan pattern superimposed. The length, line spacing, and angle of the scan are displayed above the large OCT scan. The thumbnails of the five lines are shown below the iris viewport. The large scan image on the right corresponds to the highlighted blue thumbnail and the highlighted blue scan line. Click another thumbnail image or a raster line in the iris viewport to display it as the large image. Figure 6-18 shows a High Definition Images analysis of the iris/cornea angle for an Anterior segment 5 Line Raster scan.

Note: Angle imaging may be easier using the HD Angle scan.

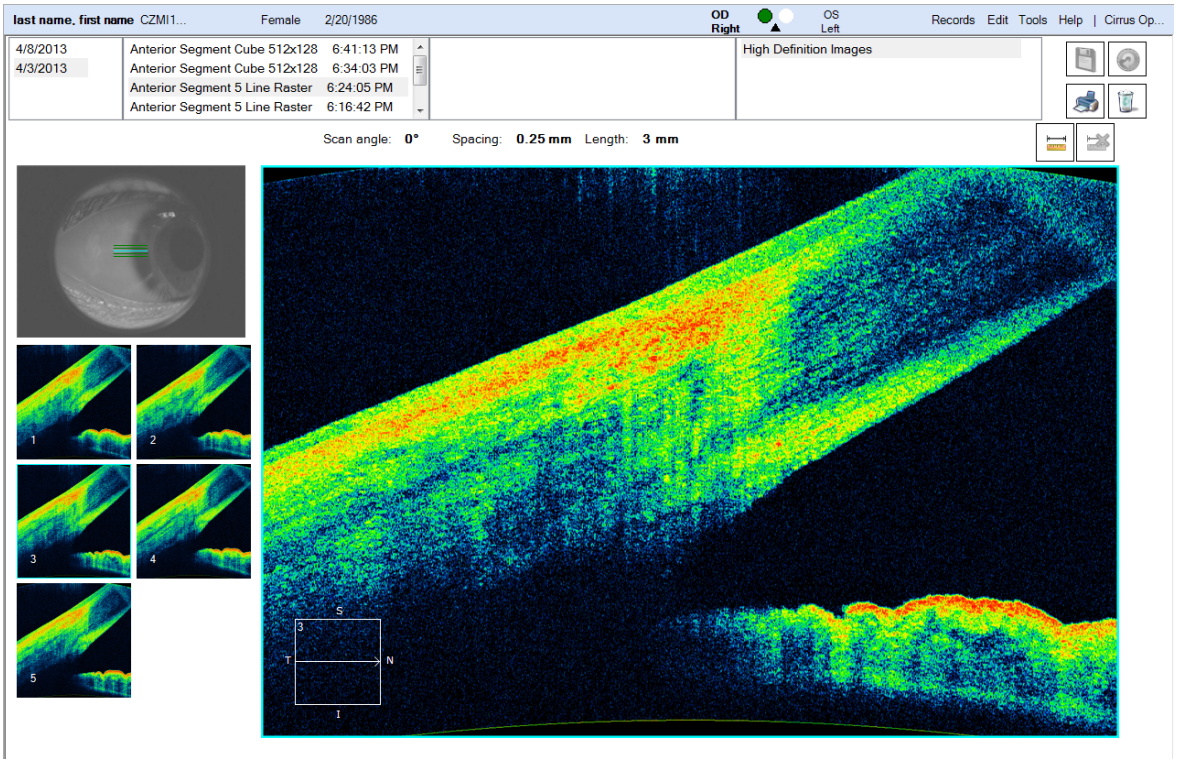


Figure 6-18: High Definition Image Analysis – Iris/Cornea Angle

Anterior Segment 5 Line Raster Analysis Image Tools

The Anterior Segment 5 Line Raster analysis screen has the following image tools:

Measurement ruler to measure corneal tissue and anterior segment structures below the cornea.

Delete all selected measurement lines.

For information on using the measurement ruler, see Anterior Segment Analysis Image Tools for Anterior Segment Cube 512x128 Scans on page 6-19.

HD Angle Analysis

The HD Angle Analysis is the only analysis available for the HD Angle scan. When you select an HD Angle scan from the ANALYZE screen scan list, the HD Angle Analysis for that scan is automatically displayed.

The HD Angle Analysis screen displays the iris viewport image and one OCT angle scan. The iris viewport image indicates the length and angle of the scan, which are also displayed above the OCT scan image.

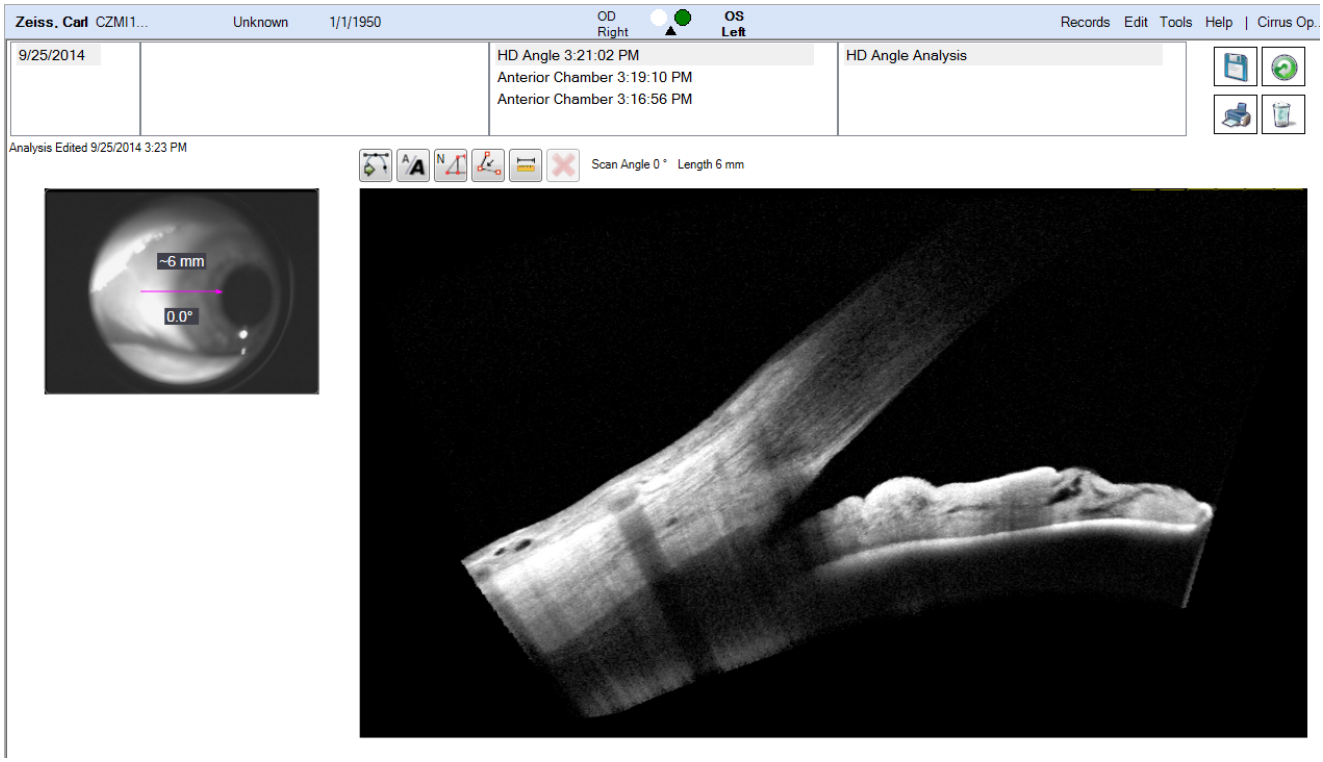


Figure 6-19:HD Angle Analysis

HD Angle Analysis Image Tools

With the exception of the Iridocorneal (IC) Angle tool, the image tools available for HD Angle analysis are a subset of those described for the Anterior Chamber Analysis, see Anterior Chamber Analysis Image Tools on page 6-19.

Iridocorneal (IC) Angle Tool

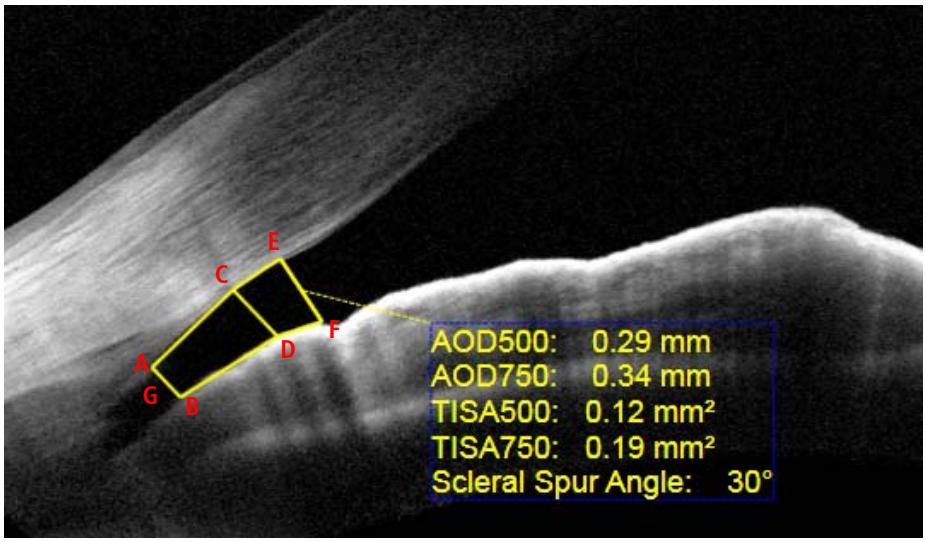


Figure 6-20: IC Angle Tool for HD Angle Scan

A Scleral Spur	D AOD 500 Iris Endpoint	F AOD 750 Iris Endpoint
B Scleral Spur Iris Endpoint	E AOD 750 Corneal Endpoint	G Recess
C AOD 500 Corneal Endpoint		

To add a left or right iridocorneal angle tool to the scan

- Click the **Add Left IC Angle** button or **Right IC Angle** button to place the left or right iridocorneal angle tool on the image.

The iridocorneal angle tool is a trapezoid that can be moved and adjusted to graphically display angle opening distance (AOD) at 500mm and 750mm, trabecular iris space area at 500mm and 750mm, and sclera spur (SSA) angle.

A table based on the dimensions of the trapezoid is displayed with values for the AOD 500 and 750, TISA 500 and 750, and SSA parameters.

To move the iridocorneal angle tool

- Move the pointer to any line on the trapezoid, and then drag the tool to an area of interest.

To resize or make angle adjustments to the IC angle tool

- Move the pointer to the end of any line on the trapezoid until it changes to a yellow circle, and then drag the end.

To place the IC Angle Tool

1. Identify the scleral spur and place point A of the IC Angle Tool at the scleral spur.
2. Adjust point C (AOD 500 corneal endpoint) to touch the corneal endothelium.
3. Adjust point E (AOD 750 corneal endpoint) to touch the corneal endothelium.
4. Adjust point F (AOD 750 Iris Endpoint) to touch the iris.
5. Adjust point D (AOD 500 Iris Endpoint) to touch the iris.
6. Adjust point B (Scleral Spur Iris Endpoint) to touch the iris.

Iridocorneal Angle Abbreviations

Abbreviation	Measurement
AOD500	Angle Opening Distance at 500 mm: Distance between C and D.
AOD750	Angle Opening Distance of 750 mm: Distance between E and F.
TISA500	Trabecular Iris Space Area 500 (mm^2): The area of the polygon defined by the sides forming a circuit through points A,C,D, and B.
TISA750	Trabecular Iris Space Area 750 (mm^2): The sum of the areas of the two quadrangles defined by the sides A, C, D, B, and C, E, F, D.
SSA	Scleral Spur Angle: This is a measure of the angle formed by CAD, that is, the angle measured at the conjunction of lines CA and AD. Note that line AD, which is not shown in Figure 6-20, is the line connecting the Scleral Spur (point A) to the AOD 500 iris endpoint (point D).

HD Cornea Analysis

The HD Cornea Analysis is the only analysis available for the HD Cornea scan. When you select an HD Cornea scan from the ANALYZE screen scan list, the HD Cornea Analysis for that scan is automatically displayed.

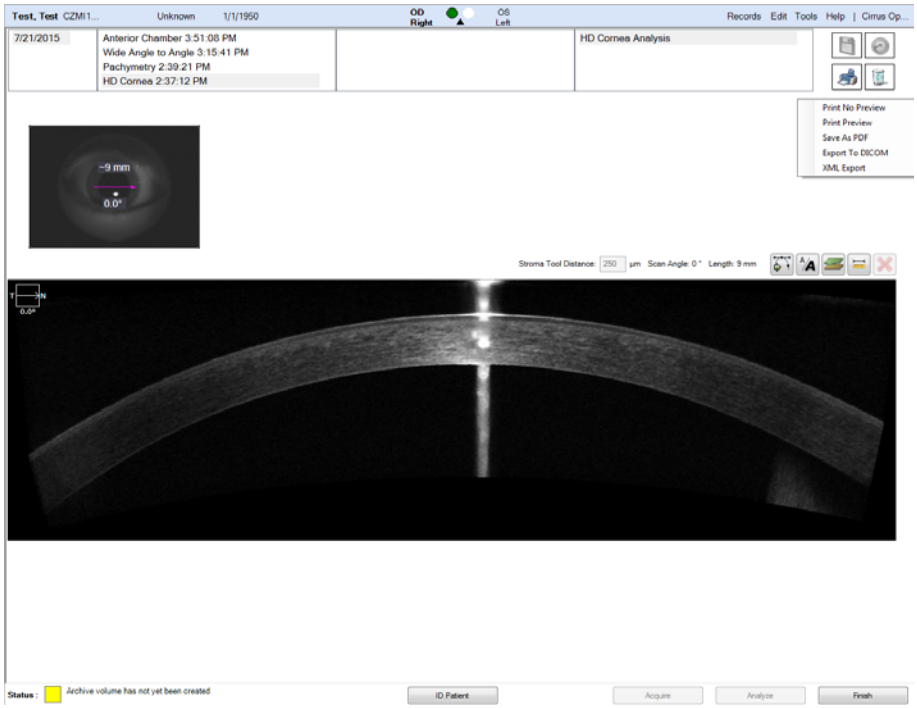


Figure 6-21: HD Cornea Analysis

The HD CORNEA ANALYSIS screen shows the iris viewport with the scan line, the length of scan, and the scan angle displayed (Figure 6-19). The length of the scan and the scan angle are also displayed above the OCT image.

HD Corneal scans are intended primarily for analysis of the residual stromal bed on post-LASIK patients.

Pachymetry Analysis

The Pachymetry Analysis is the only analysis available for the Pachymetry scan. The Pachymetry Analysis uses the 24 radial scan lines of the Pachymetry scan to display a color-coded map of the cornea (Figure 6-22).

Selecting Pachymetry Scans for analysis

To select Pachymetry scans for analysis, do one of the following:

- To automatically select a Pachymetry scan for one eye and the most recent Pachymetry scan for the other eye taken on the same day, select one Pachymetry scan from either scan list, and then click **Pachymetry Analysis**.
- To manually select the Pachymetry scans for each eye you want to compare, select a Pachymetry scan from each scan list, and then click **Pachymetry Analysis**.
- To display a single pachymetry map if only one eye has Pachymetry scans, select one Pachymetry scan from the list, and then click **Pachymetry Analysis**.

Color Scale Display Options

On the Pachymetry analysis screen, a color scale is displayed to the left of each pachymetry map. The following color scale options are available when you right-click on a color scale. The option you choose is applied to both scans and is saved with the analysis.

Auto: Displays thinner areas of the cornea in red and thicker areas in blue.

Standard (default setting): Displays colors that always represent the same thickness so that blue is 750um and red is 350um.

Custom: Displays a color map based on the minimum and maximum thickness values defined in the COLOR SCALE dialog, which opens when you click **Custom** from the menu list.

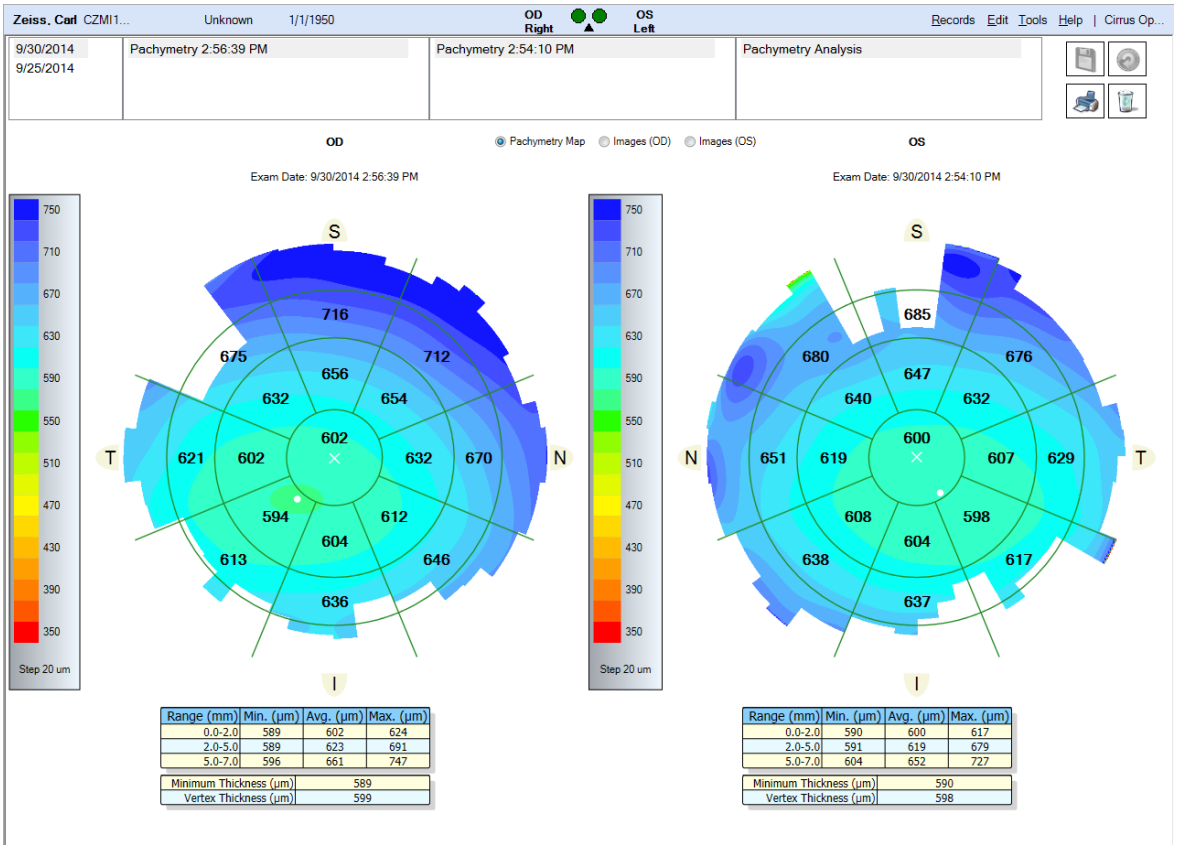


Figure 6-22: Pachymetry Analysis

View and Mark Corneal Thickness Locations

X=-290.3 Y= 175.9 Thickness=559.8

On a Pachymetry map, move the mouse over any point on the map to see the corneal thickness (micrometers) calculated at that point and the location (micrometers away from the center of the map) in radial (distance and angle) coordinates above the map (shown on the left). Click a point on a pachymetry map to mark a thickness value at that location—this value is printed on reports. Right-click a map and check **Clear User Selection** to clear the thickness marker. You can also deselect **Show Mean Only**, which is the default setting, to show only the mean value in each sector or **Hide Data** to hide all data values on a map.

Cornea Thickness Data Tables

The data table displayed below the pachymetry maps contains thickness measurements for the zones on the pachymetry maps. Minimum, average, and maximum thickness measurements in micrometers for the three radial zones appear. The zone range is defined in millimeters away from the center of the map. The central ring is from 0 to 2 mm, the inner ring is from 2 to 5 mm, and the outer ring is from 5 to 7 mm. The zone grid is centered on the corneal vertex (the intersection of the visual axis with the corneal surface). The black "X" shows the location of the vertex. The white dot on each map in Figure 6-22 shows the location of minimum corneal thickness. This value is also reported in the data table.

Viewing Thumbnails of Cornea Scans

To view the 24 thumbnail scans used to generate the Pachymetry scan for an eye, above the pachymetry maps in the center of the screen, select either **Images (OD)** or **Images (OS)**. The anterior surface of the cornea is highlighted with a green line and the posterior surface of the cornea is highlighted with a red line (Figure 6-23). To view a thumbnail in full screen, double-click on the thumbnail image, and double-click again to return to the thumbnail view.

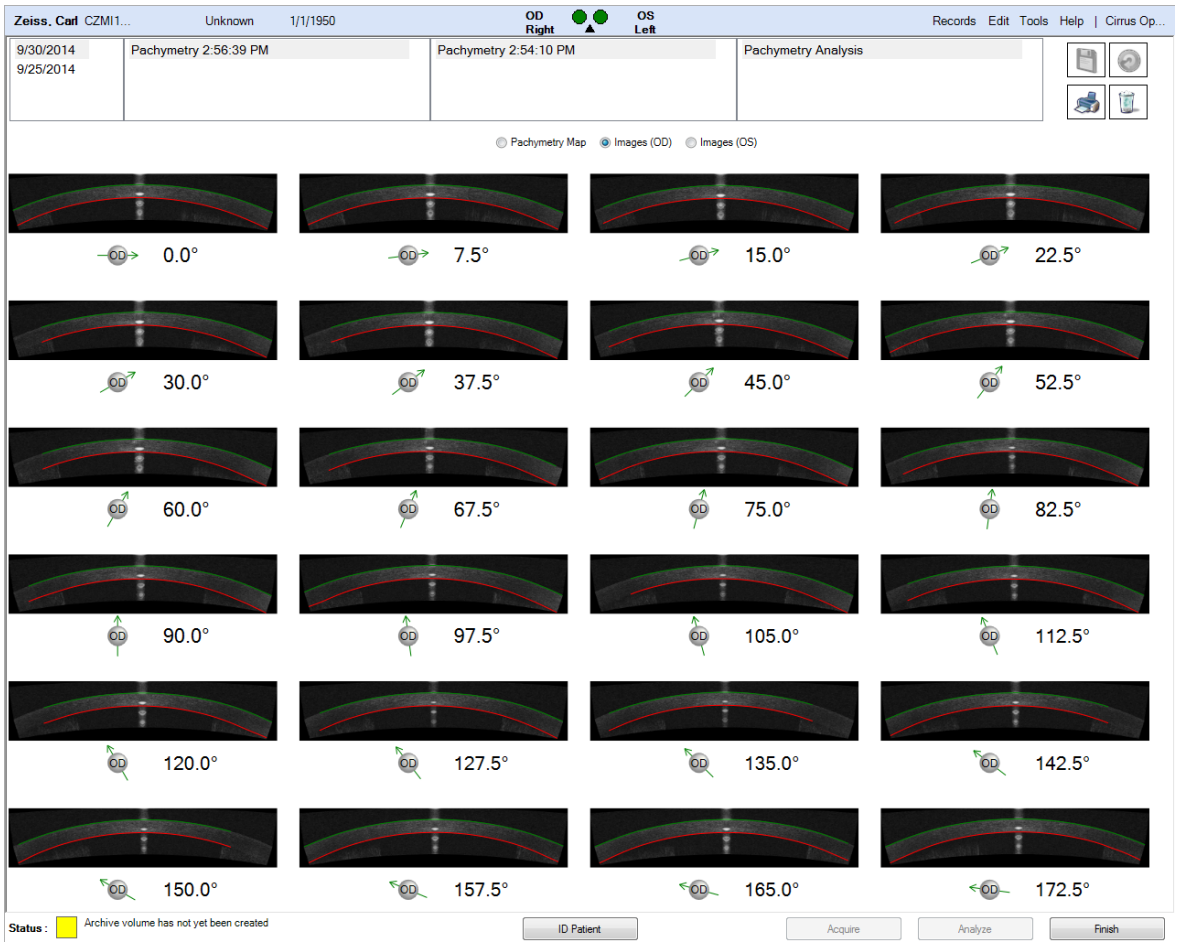


Figure 6-23: Pachymetry Thumbnails

Wide Angle to Angle Analysis

The Wide Angle to Angle analysis is the only analysis available for the Wide Angle to Angle scan. When you select a Wide Angle to Angle scan from the ANALYZE screen scan list, the Wide Angle to Angle analysis for that scan is automatically displayed.

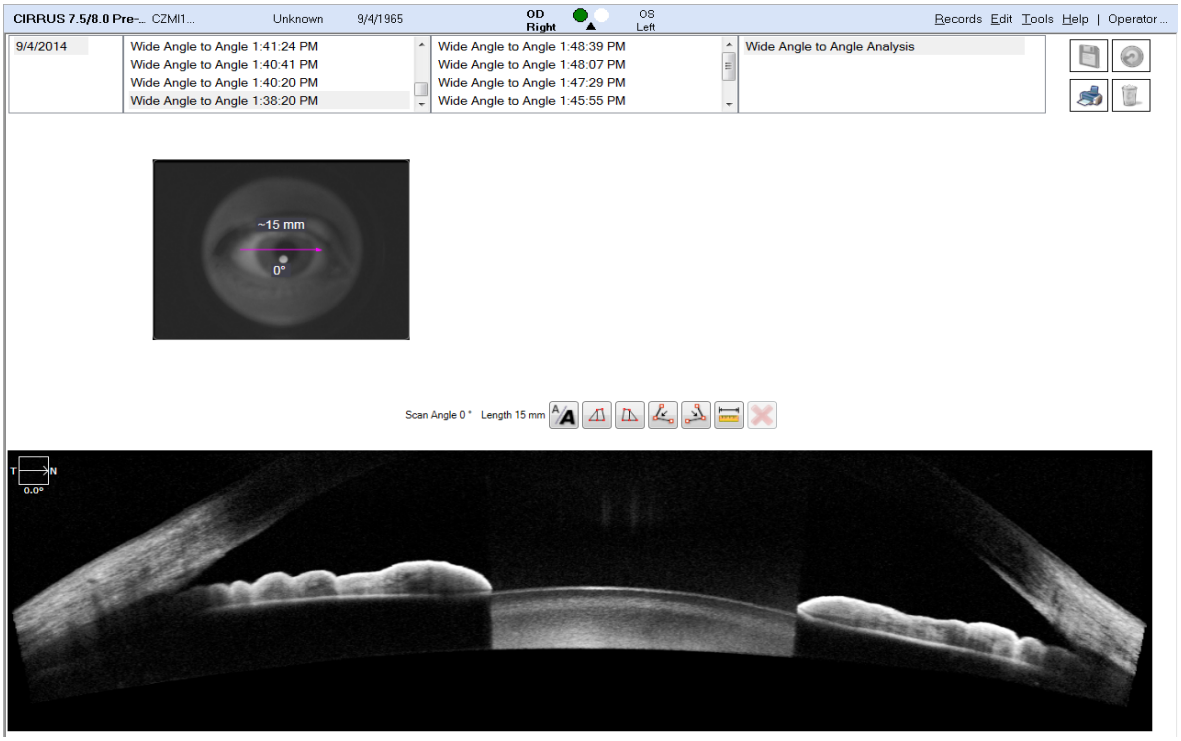


Figure 6-24:Wide Angle to Angle Analysis

The Wide Angle to Angle analysis displays the iris viewport image and one wide angle scan. The iris viewport image indicates the length, and angle of the scan, which are also displayed above the OCT scan image.

Wide Angle to Angle Analysis Image Tools

With the exception of the Iridocorneal (IC) Angle tool, the image tools available for Wide Angle to Angle analysis are a subset of those described for the Anterior Chamber Analysis, see Anterior Chamber Analysis Image Tools on page 6-19. The Iridocorneal Angle tool is also available for the HD Angle scan. For information on its use, see Iridocorneal (IC) Angle Tool on page 6-29.

Anterior Segment Reports

Printing out any Anterior Segment analysis is done in the same way as posterior segment analysis (see Reports and Printing on page 4-45). Reports for all anterior scans are stock printouts that include all the information on the ANALYZE screen when you click **Print**.

1. **Gait mat installation and training**

The Protokinetics Zenomat will be dispatched from the company in two boxes. Once they arrive, they need to be stored without opening until the technical support person arrives to set it up the first time. Training will be organized to coincide with this.

Contact information of Protokinetics technical support engineer.
Patrick Roscher
Chief Technical Support Engineer
patrick@protokinetics.com
651-357-5949
www.protokinetics.com

2. **Routine care and maintenance of mat and accessories**

The Zenomat will be placed in the FHS corridor close to the wall and cordoned off with a chain post or stanchion. The mat will be damaged if heavy items are dragged over it or if it is mopped or flooded. The accessories including the laptop and wires will be stored under lock and key. The table (with wheels) on which the laptop is placed will be kept in the adjacent exam room.

On the day of testing, prior to the participants arrival, the mat will be positioned in the center of the corridor and the stanchion removed. People can walk over the mat while crossing the corridor as long as they are not wearing sharp heels.

The position of the mat and the starting and ending line will be marked with yellow tape - this tape has to remain until all gait testing for the cohort is over.

About 10 minutes prior to the testing procedure, the person doing the testing will cordon off the area with stanchions and a stop sign so that people cannot walk in and obstruct testing. The table will be moved into position. The gait mat will be connected to the laptop and the Zeno software initialized by the trained assessor.

After the testing is over, the stanchion and stop sign will removed and people allowed to cross until the next participant arrives for testing.

After all the testing for the day is over, the mat will be disconnected, removed to the side and cordoned off again.

3. Gait testing procedure:

Eligibility:
All participants of the Offspring cohort are eligible for gait assessment unless they are on a wheelchair and not able to walk at all. Participants who need a cane of walker to walk the short distance can use them.

Safety:
All testing will be done after the participant understands the procedure and deems it safe (see script). If participant thinks it might be unsafe, do not test. Even if the participant deems the test safe, the possibility that that an older participant with difficulty walking and poor balance may fall remains. Gait assessment will typically be performed by a single person who will stay near the laptop and will not follow the participant during the walk. So, when an older participant with difficulty in walking, who might fall, is to be tested, another research assistant should be called to follow behind (out of sight and outside the mat) to provide quick support in case of loss of balance.

Testing:
The participant will be escorted to the gait testing area. The tester will follow the gait mapping script. At the end of testing, the tester will verify that steps have been captured on the Zeno folowing which the participant will be escorted to the next test. The tester will record on the FHS redcap that gait was tested. (yes/No) and reason why not tested.

4. Cleaning and saving data

Review of Zeno steps and cleaning will be done after all testing is completed for the day. The tester will look through each pass and delete half-steps, cane marks etc. After cleaning, the 2 excel files (ID_normal pace, ID_dual task) will be saved on a folder named with the ID on the laptop. At the end of the days testing, the tester will copy the new data onto a password protected hard drive on the computer that can be accessed remotely.

The laptop that connects to the gait mat will not be connected to the internet to prevent Microsoft and other software updates that interfere with the Protokinetics software.

5. Quality Control procedures

All testing will be done by trained testers who will be trained and certified in gait testing and use of Zeno software by Mini Jacob. Testers will also attend the training session with the Protokinetics representative. Mini will be available by phone for answering queries from testers and FHS research staff. She will also periodically assess the testing by observing testing procedure. She will also access gait data remotely once in 2 weeks for quality control.
Mini Jacob (412-996-8778) email: jacobm@uthscsa.edu

Prior to testing:

Make sure that the participant is wearing comfortable shoes.

Wear quiet shoes and remove anything that makes noise from your pockets (keys, coins) while conducting this test. Sounds can provide cues to the participant regarding the speed at which to walk, i.e., you will be pacing the participant.

Set up the Zenomat prior to testing, login and scan the walkway.

You will also need a timer, the gait mapping script, a dual task response sheet, a writing board and a pen for this test.

GAIT MAPPING SCRIPT

Practice Walk

"*This an electronic gait-mat which records your footsteps when you walk on it. This is your starting line. I would like to you walk at normal pace down the walkway just as if you were walking down the street to go to a store. If you need to use a walking aid to walk this distance you may use it. Be sure to only step in the center brown colored section of the gait-mat. Keep walking beyond the end of the gait-mat to the finishing line, turn beyond the finishing line and come back. When you cross the mat once, that is called a "Pass" – so you will be walking 2 passes. I will walk with you. Do you think this is safe?*

If participant does not think this is safe, do not continue with testing.
If participant responds that it is safe, have the participant stand at the starting point. Position yourself behind and to the side of the participant. This walk will not be recorded.

This first trial will be for practice. Do you have any questions?
When I want you to start, I will say "Ready, begin".
When the participant acknowledges this instruction, say *"Ready, begin".*

Walk behind and to the side of the participant, out of his/her visual field and outside the mat. Cross participant after he/she reaches finishing line, wait for them to start back and follow, out of sight.

Single Task Normal Pace Walk

"Very good. Now I would like you to walk on the gait-mat at your usual pace again, this time I will record it. I would like you to do 4 passes - go forward to the finishing line, turn around beyond it and come back to the starting line, and then do that once more. When I want you to start, I will say "Ready, begin".

When the participant acknowledges this instruction, “start walk” on the laptop, position yourself behind and to the side of the participant and say *“Ready, begin”.*

Walk behind and to the side of the participant, out of his/her visual field and outside the mat. Cross participant after he/she reaches finishing line, wait for them to start back and follow, out of sight.

When the participant finishes 4 passes, “End Walk” on the laptop. Save walk, enter participant ID, gender, and enter memo as “Normal Pace”.

Dual Task Walk Overview

“Very good. Now I am going to ask you to walk down the gait-mat at your usual pace as you did previously. However, this time I am going to ask you to perform a mental task at the same time. Pay equal attention to walking as well as doing the task accurately. You may find yourself slowing down during the task or stopping to think but try to continue walking at your normal pace as much as you can. You will walk 1 pass. Here is the task.”

Dual Task (Phonemic Fluency)

“While you walk down the gait-mat at your normal pace, I would also like you to tell me as many words as you can think of that begin with a specific letter of the alphabet. For example, if I say B you could give me: Battle, Bad, Bed… I don’t want you to use words that are proper names like Boston, Bob or Buick. Also, do not use the same word again but with a different ending, such as Bake and Baking.
Any questions? Remember to pay equal attention to walking and talking.
Begin when I say the letter.

Ensure participant is positioned at the starting line. “Start Walk” on the laptop. Position yourself behind and to the side of the participant.
Ready? The letter is L. Begin.”

Start timer. Walk behind and to the side of the participant, out of his/her visual field. Record the words. Stop timer when participant crosses finishing line. Note time.

If the participant stops walking OR ceases to provide a response for 15 seconds, provide the appropriate response “*Please continue walking as you provide responses*” OR “*Tell me all the words you can think of* starting with L”. When the participant finishes, “End Walk” on the laptop and enter memo as “Dual Task”.

FHS Brain Health Ancillary Study: Dual Task (Phonemic Fluency -letter L) Responses

Participant ID:

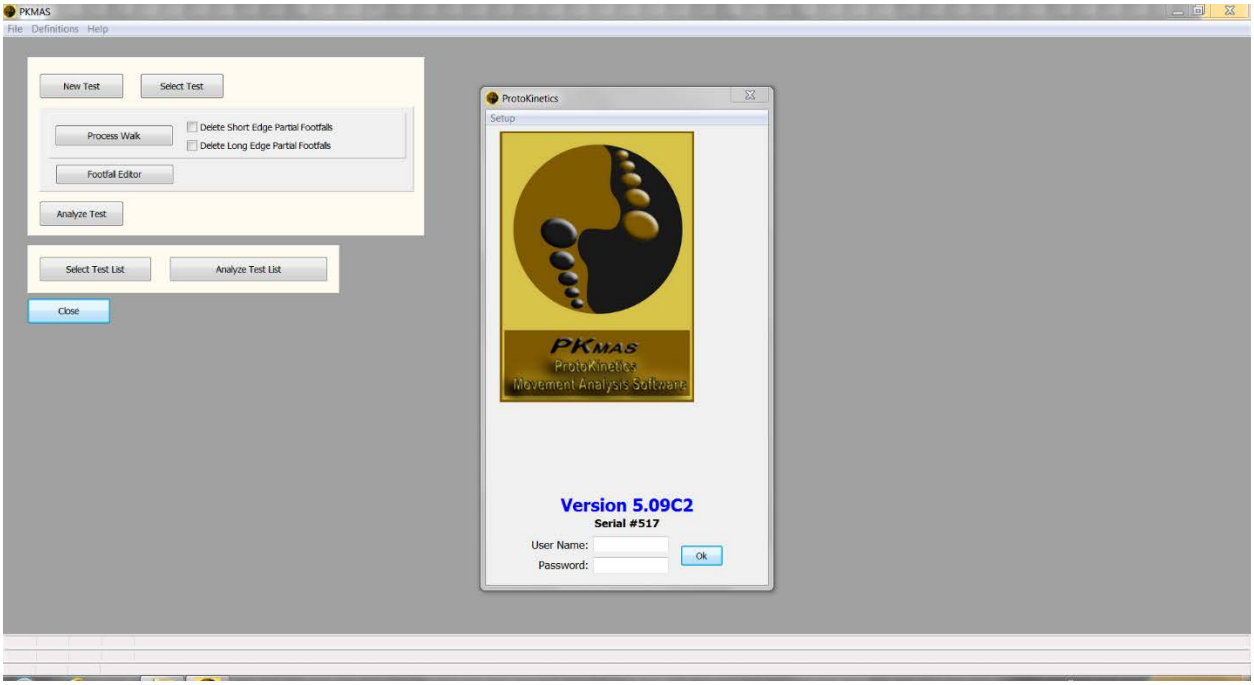
Time (from "Begin" to crossing yellow finish line):

Total number of correct words:

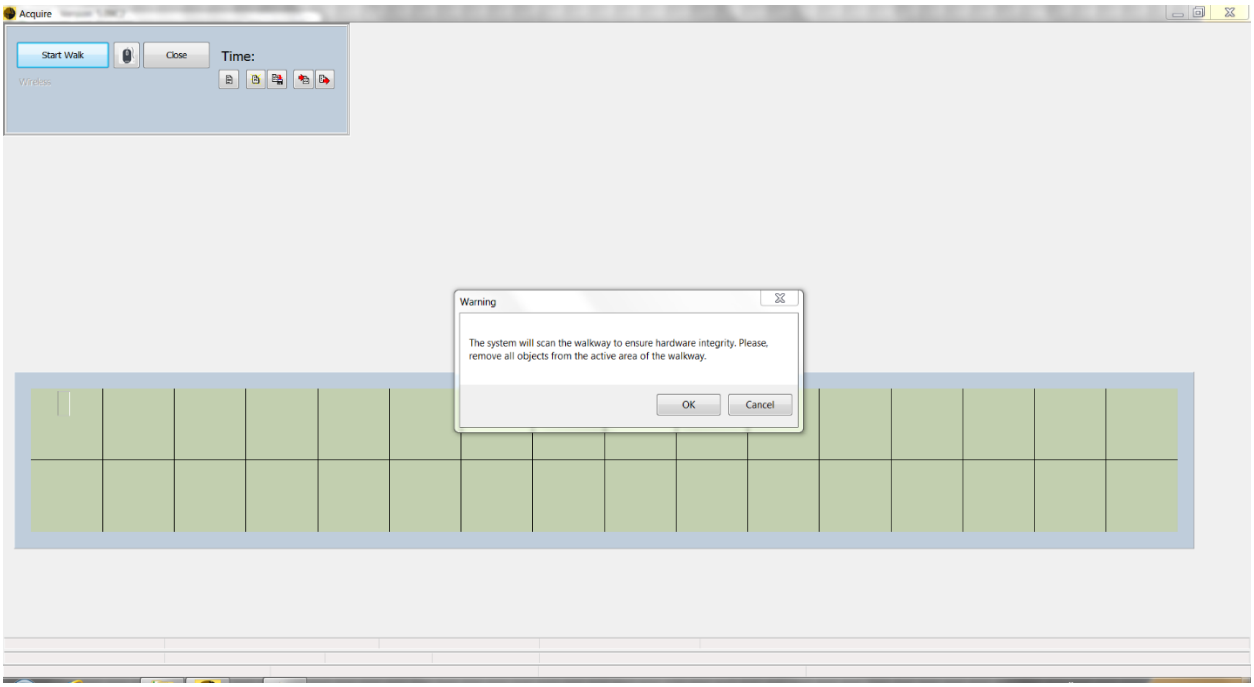
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	

Testing

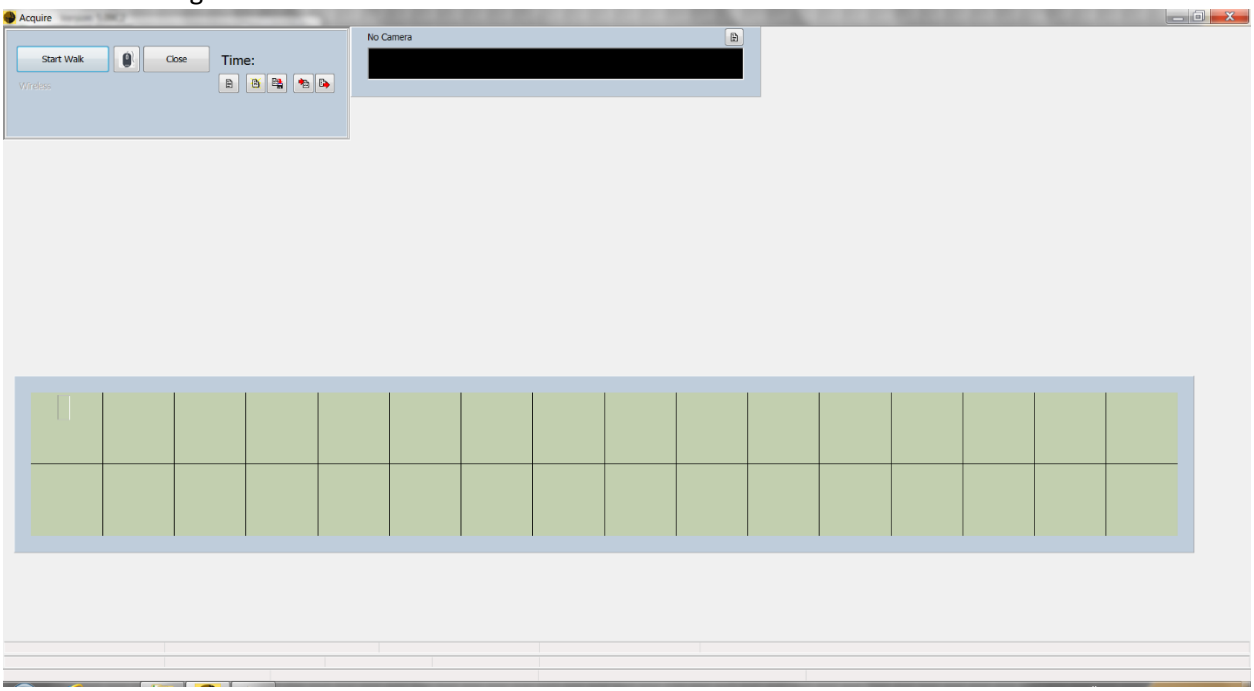
1. Double click on pkmas icon, login screen pops up



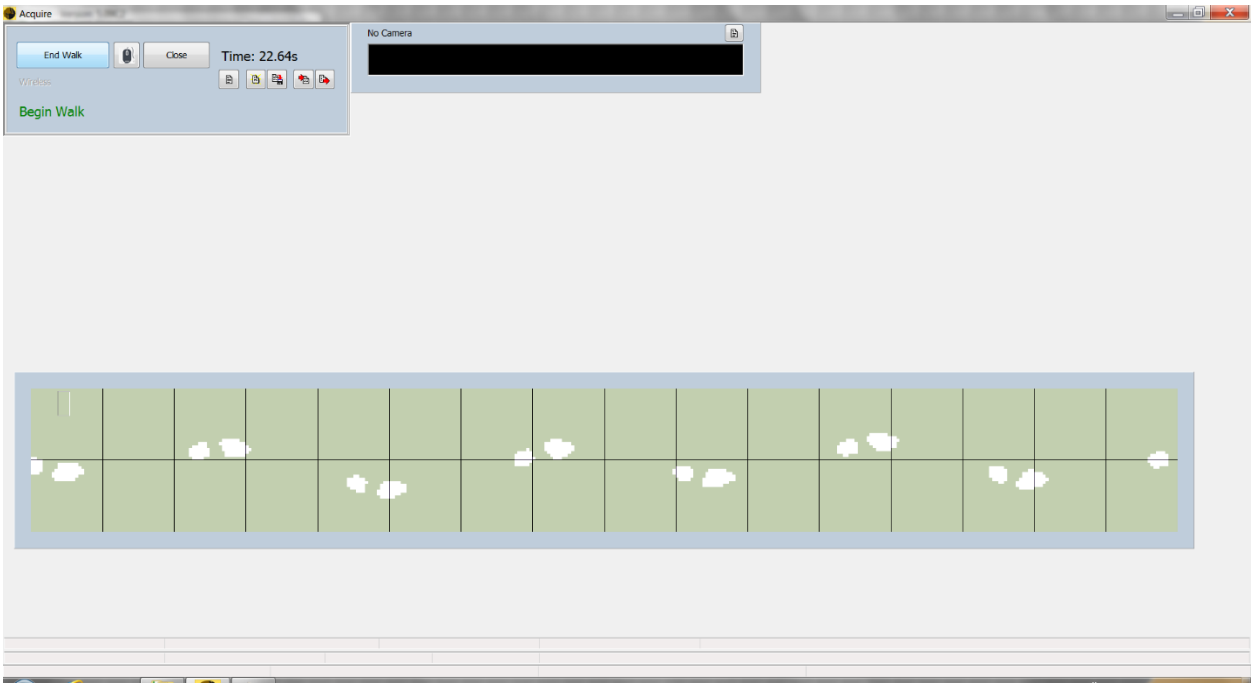
2. Click on New test, scan screen opens



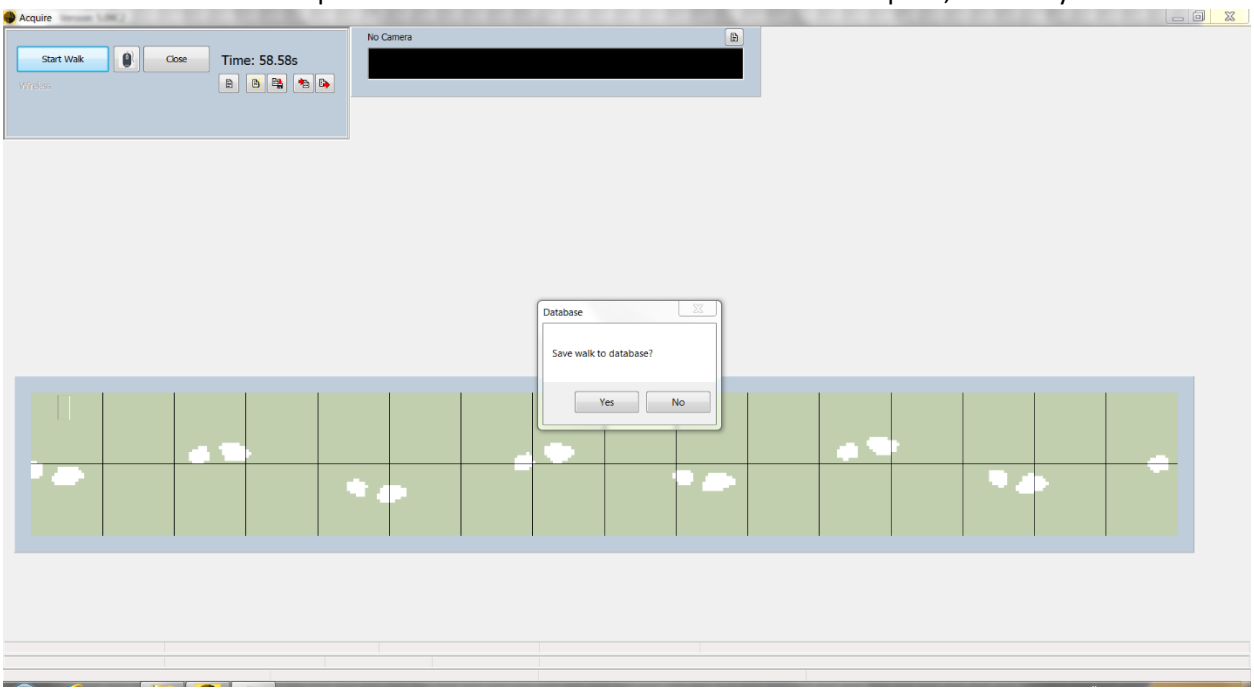
3. After scanning -



4. Give Instructions, start walk



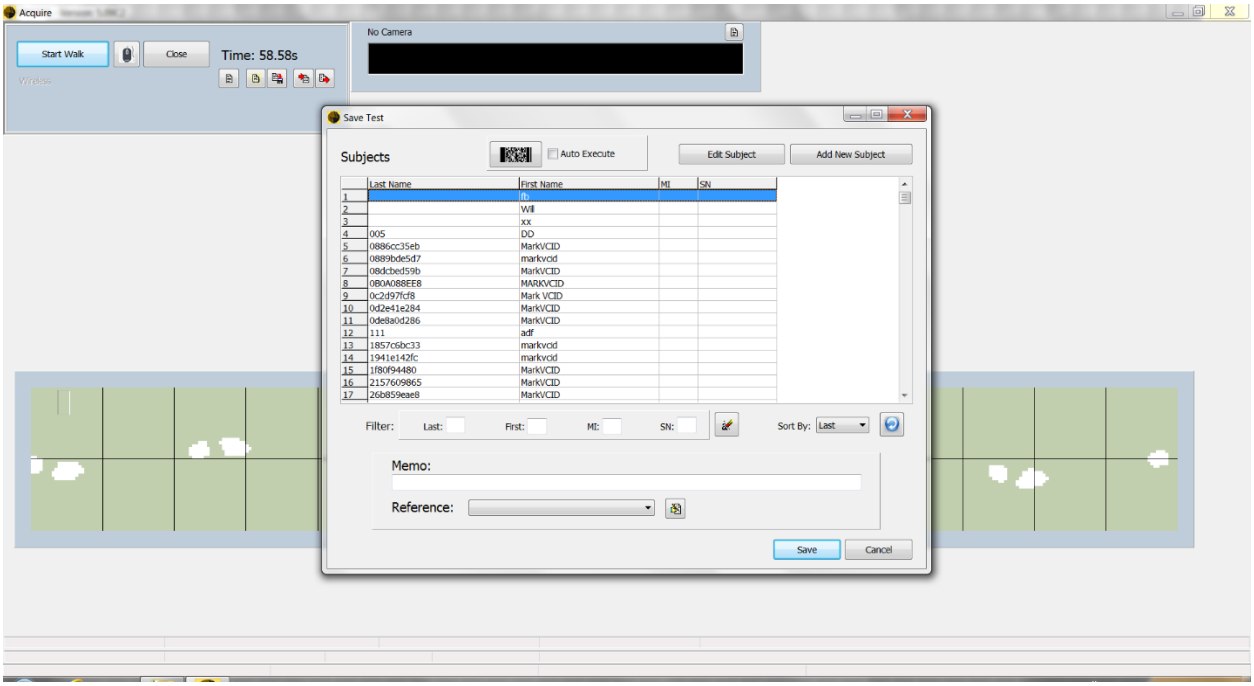
5. Click on End walk when passes are over. Save walk to database screen opens, choose ‘yes’.



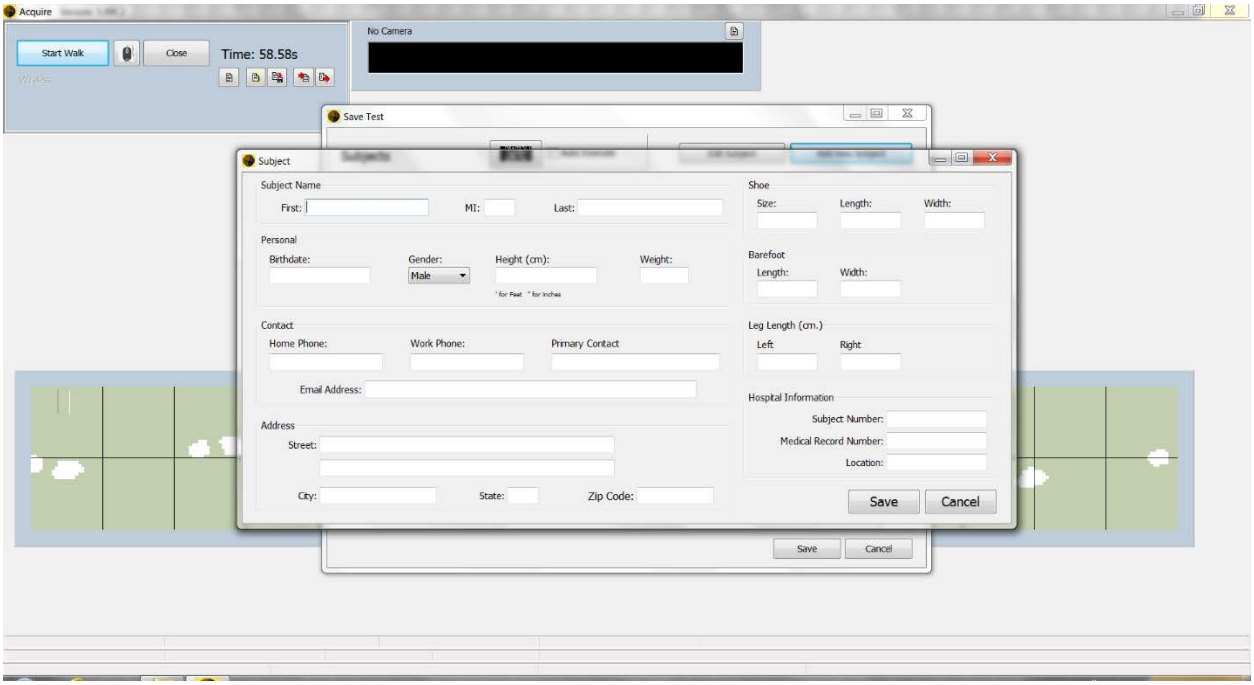
6. Save test screen with Subject list opens

*Important – DON’T hit Save here!

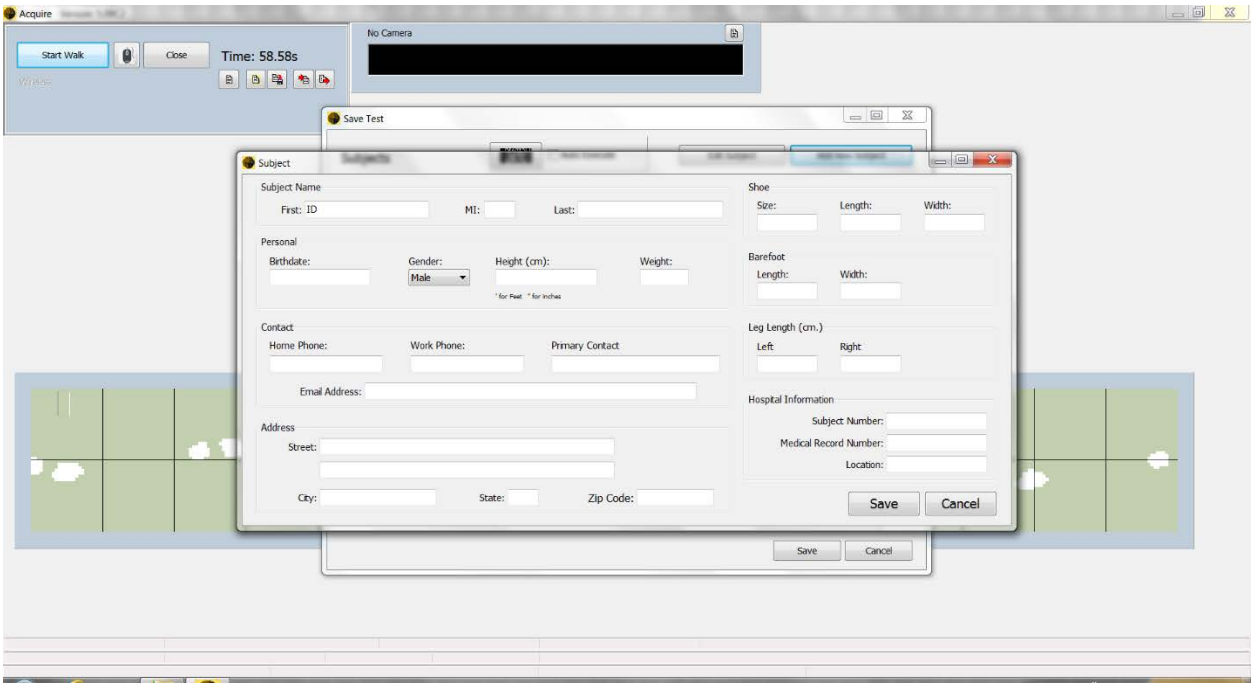
Choose ‘ADD new Subject”



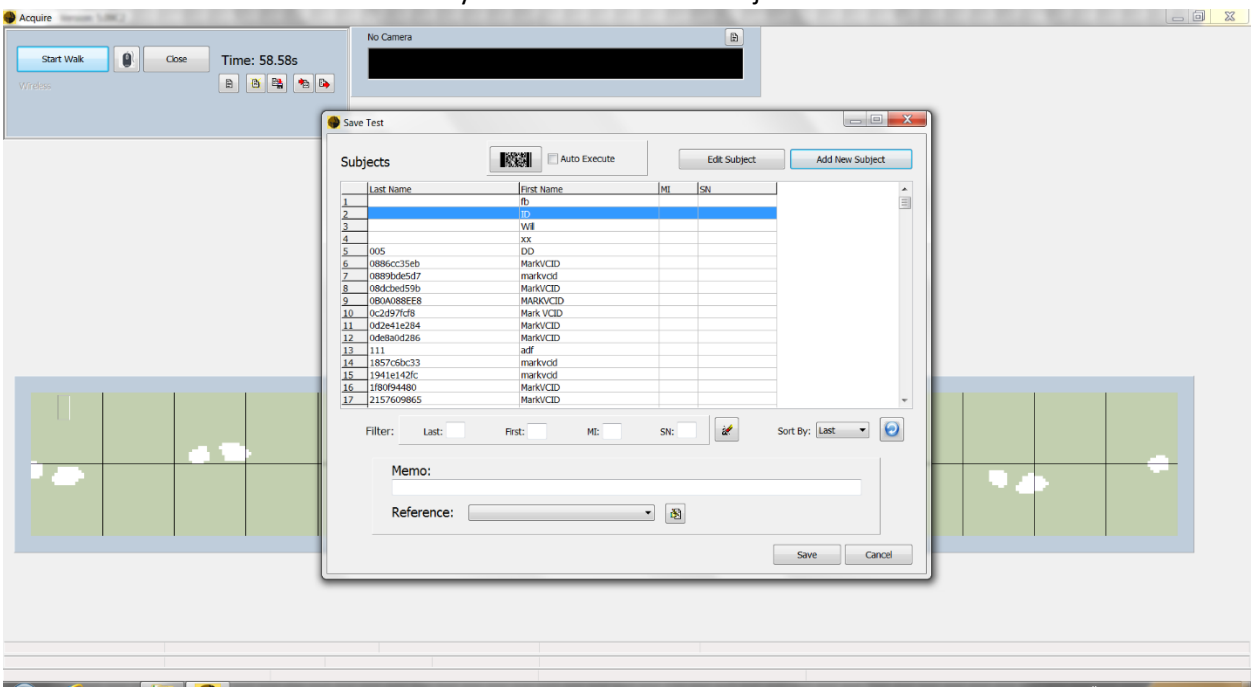
7. Add new subject – Subject screen opens



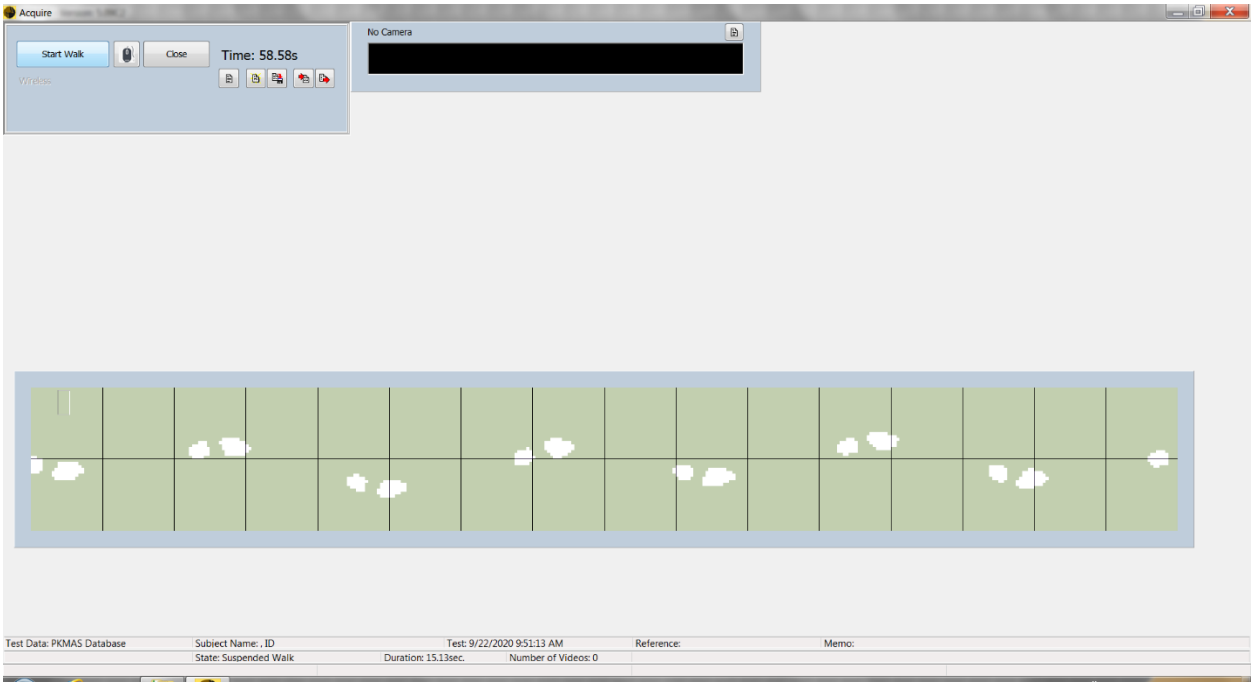
8. Enter ID and gender – manually entered, hence check very carefully and save.



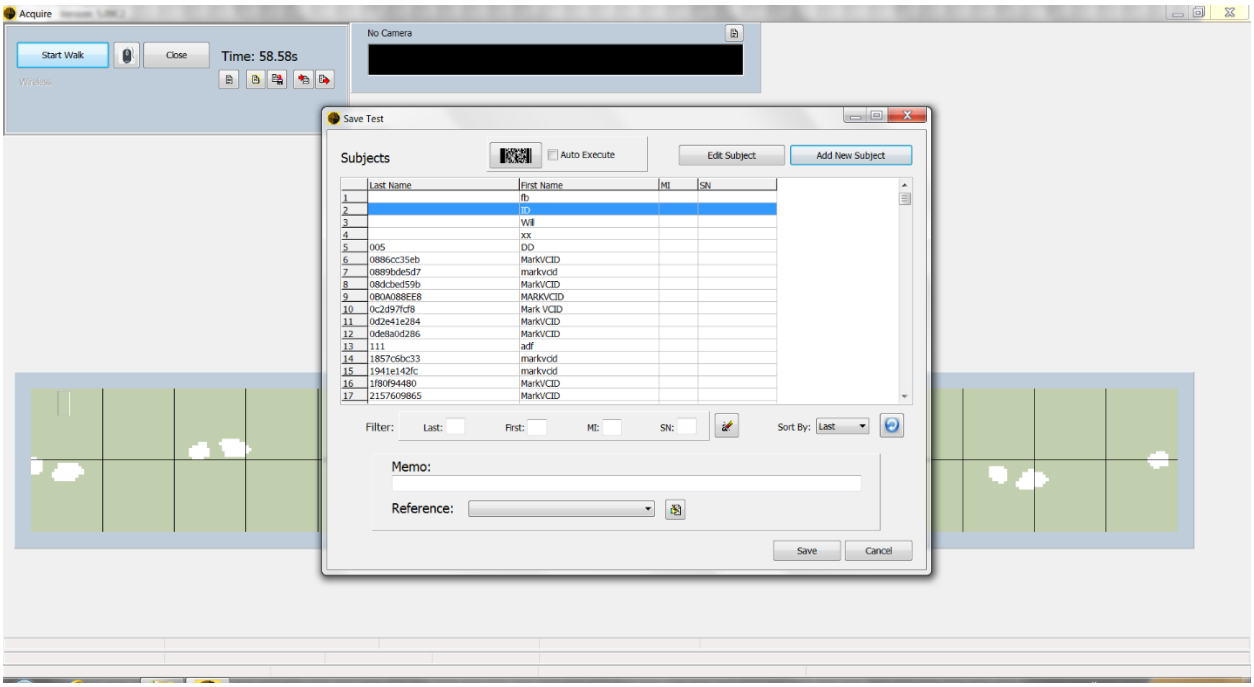
9. Back to the Save test screen – now you can see the new Subject. Save!



10. Back to Start walk screen. Start the next test- dual task here.

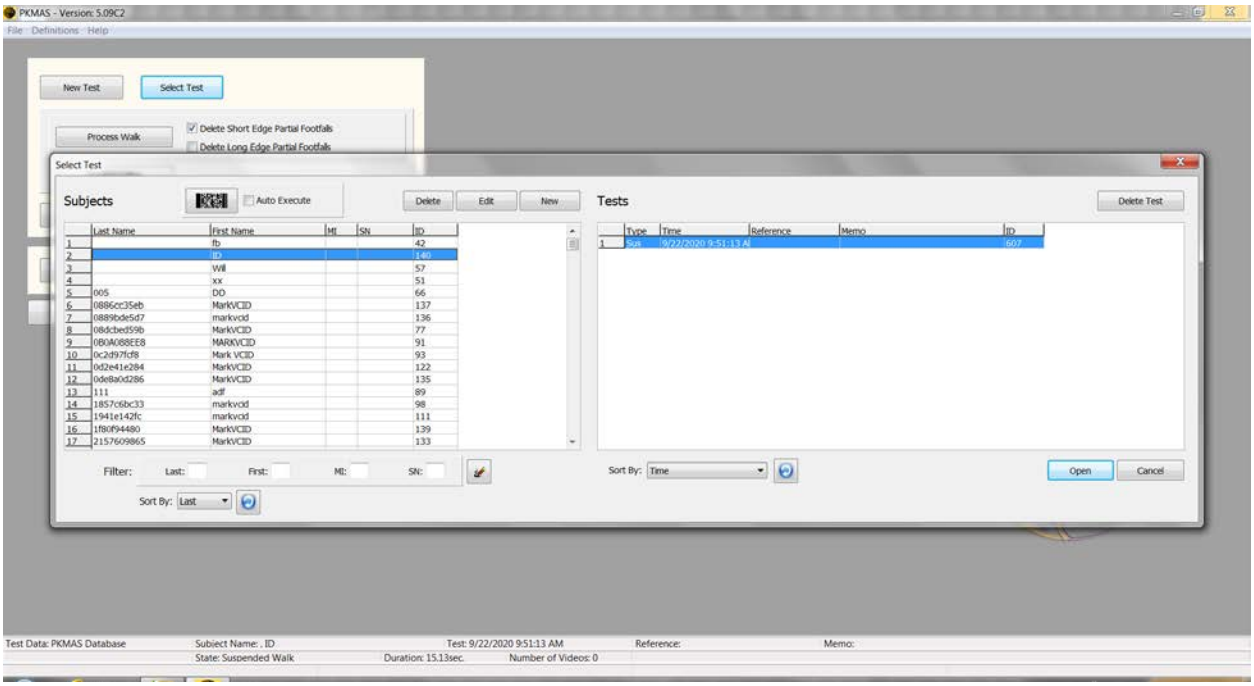


11. End walk, save walk to database. Save the file to the same subject. Ensure that the proper subject is highlighted and click save.

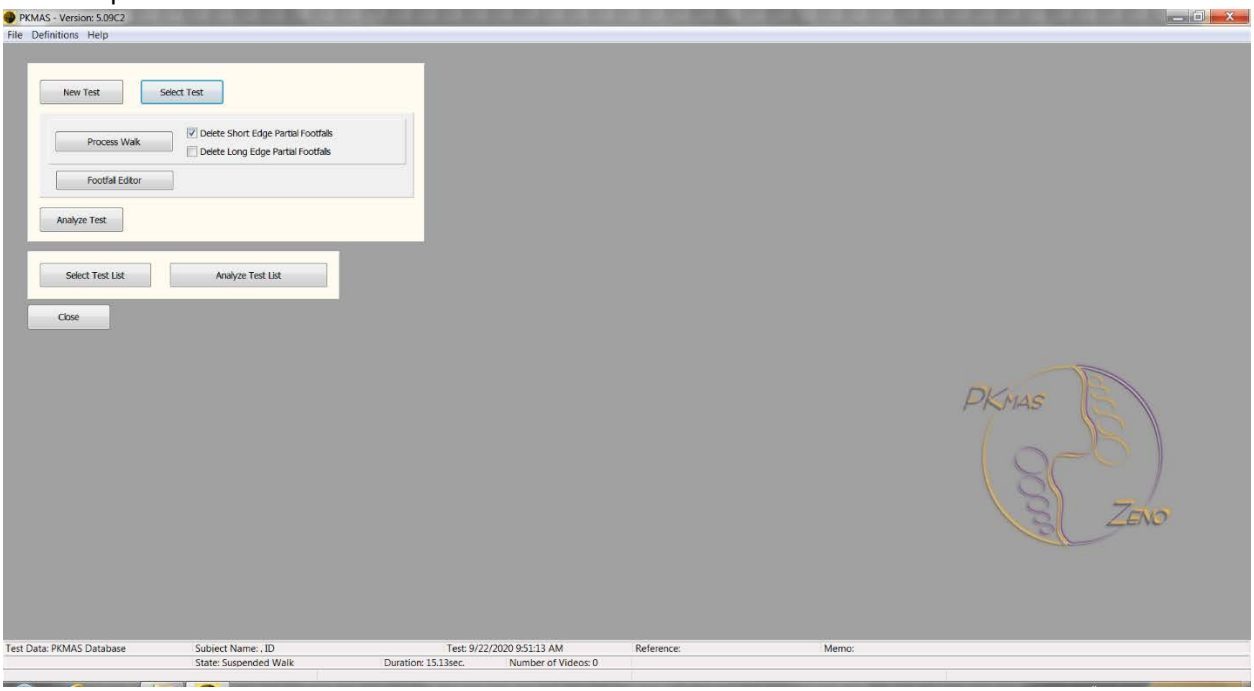


Processing the walk: can be done after all testing is over

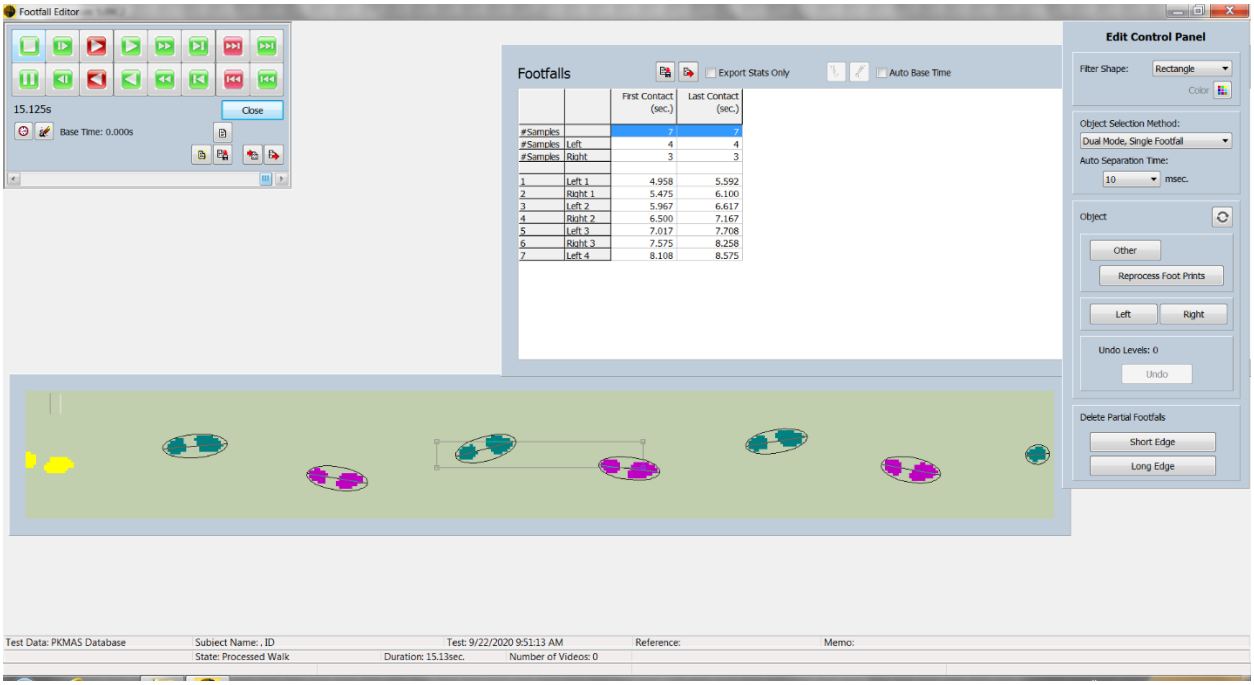
1. Select the right test and click open



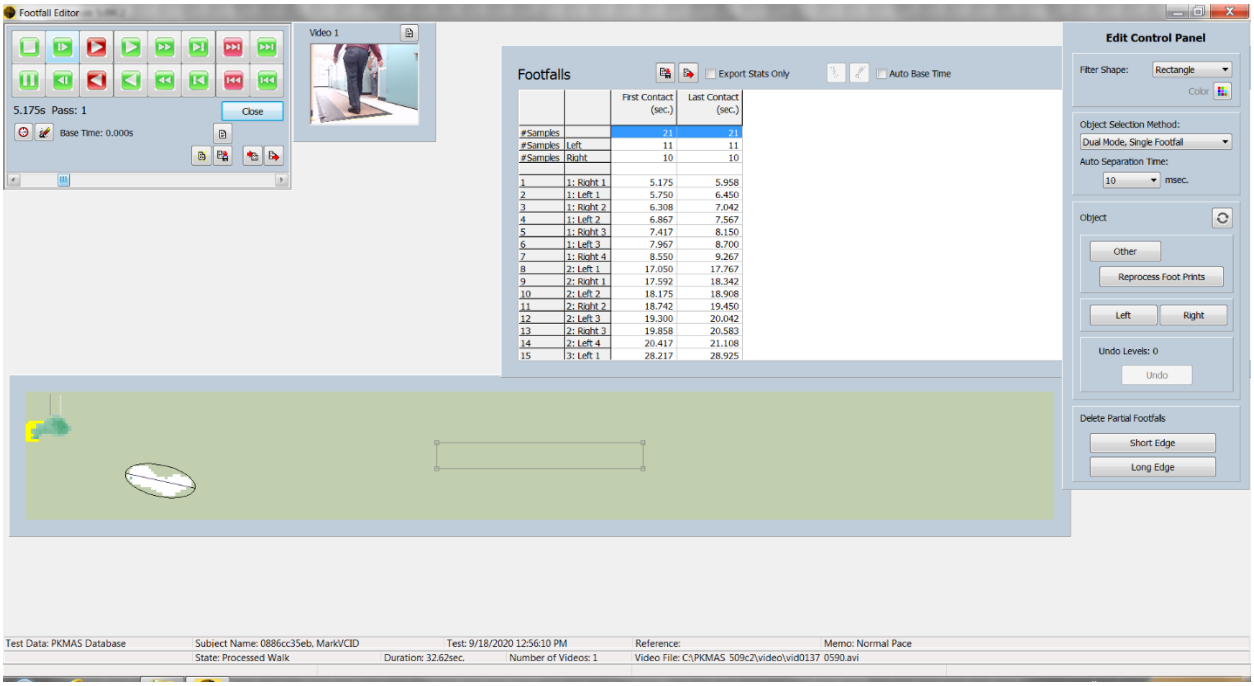
2. Select process walk button



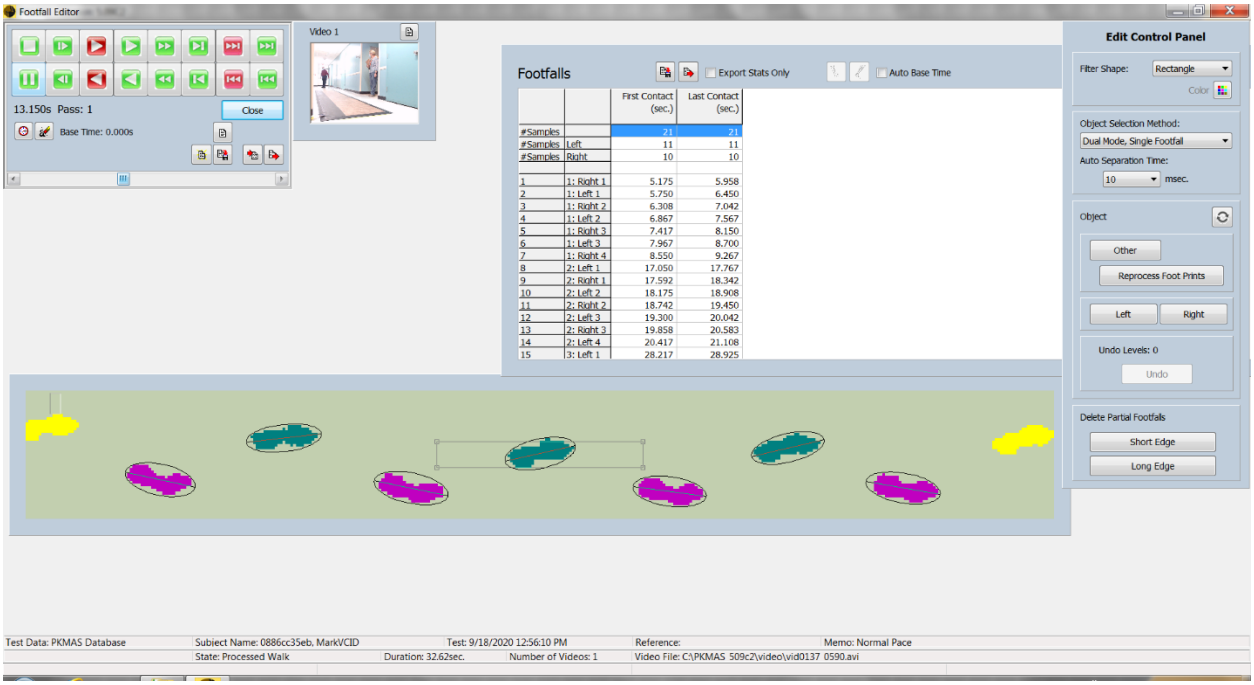
3. Process Walk screen opens



4. First Step button

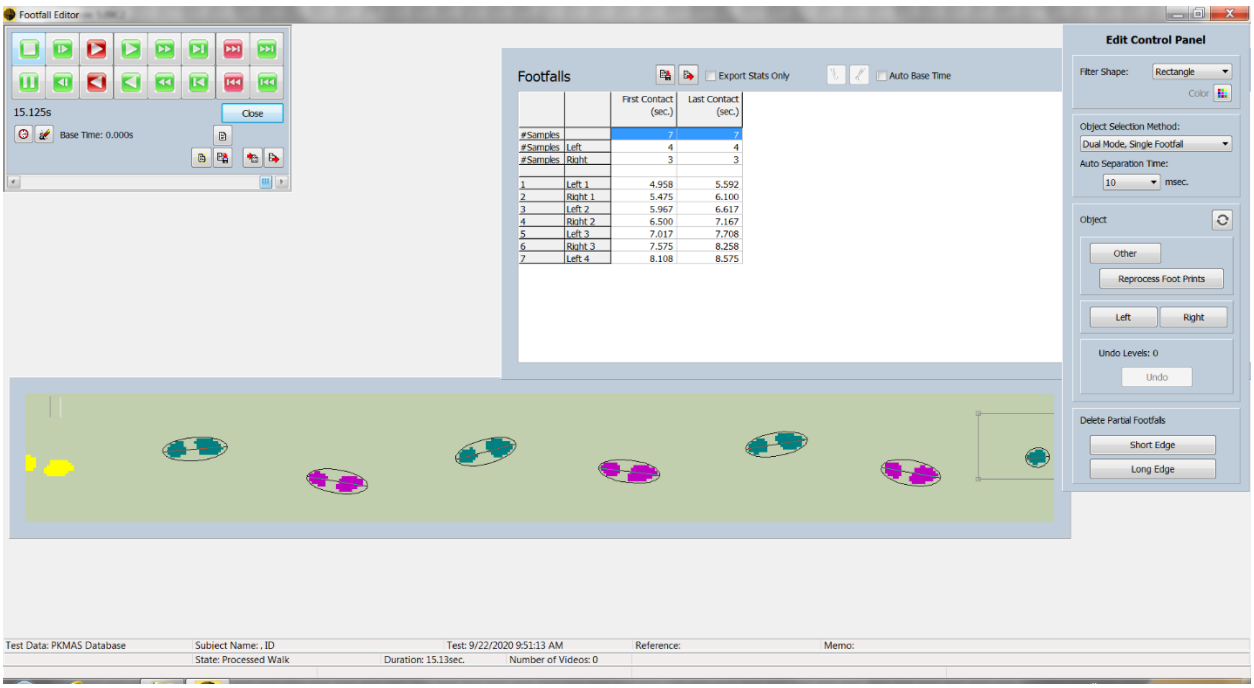


5. End of pass button shows complete pass

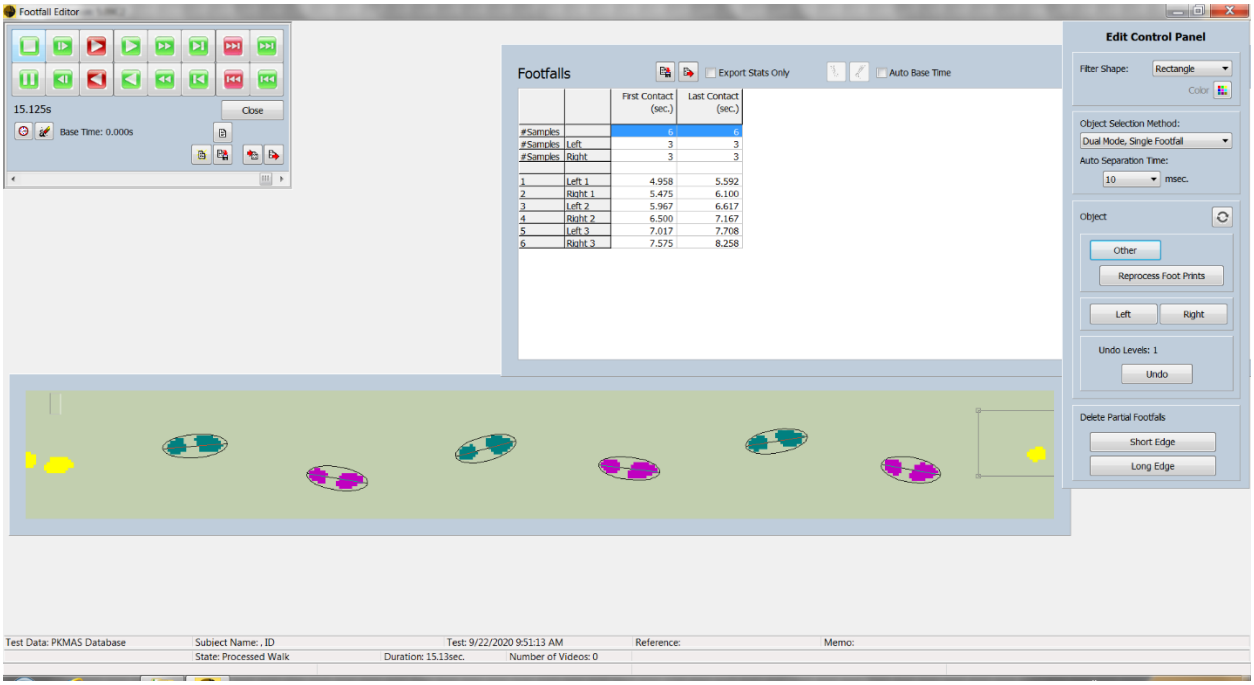


6. Check for partial footsteps even if ‘delete partial footfalls’ is checked

Go pass by pass by clicking on ‘End of Pass button’



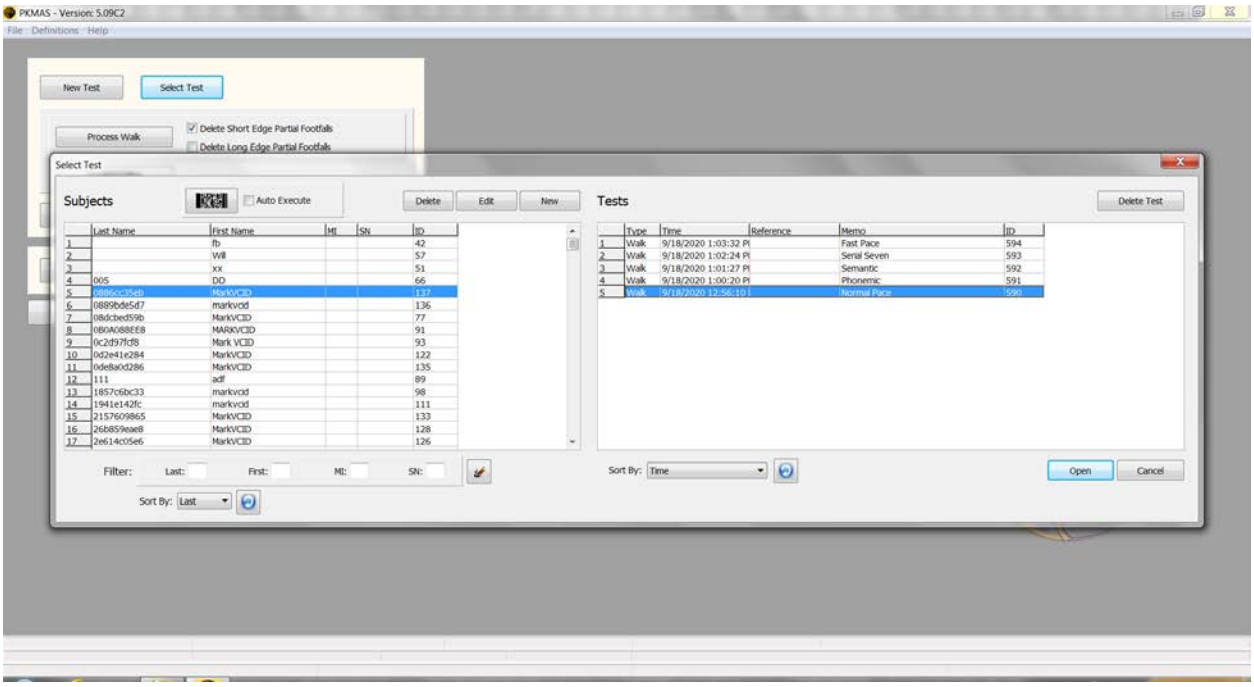
5. Appearance after editing



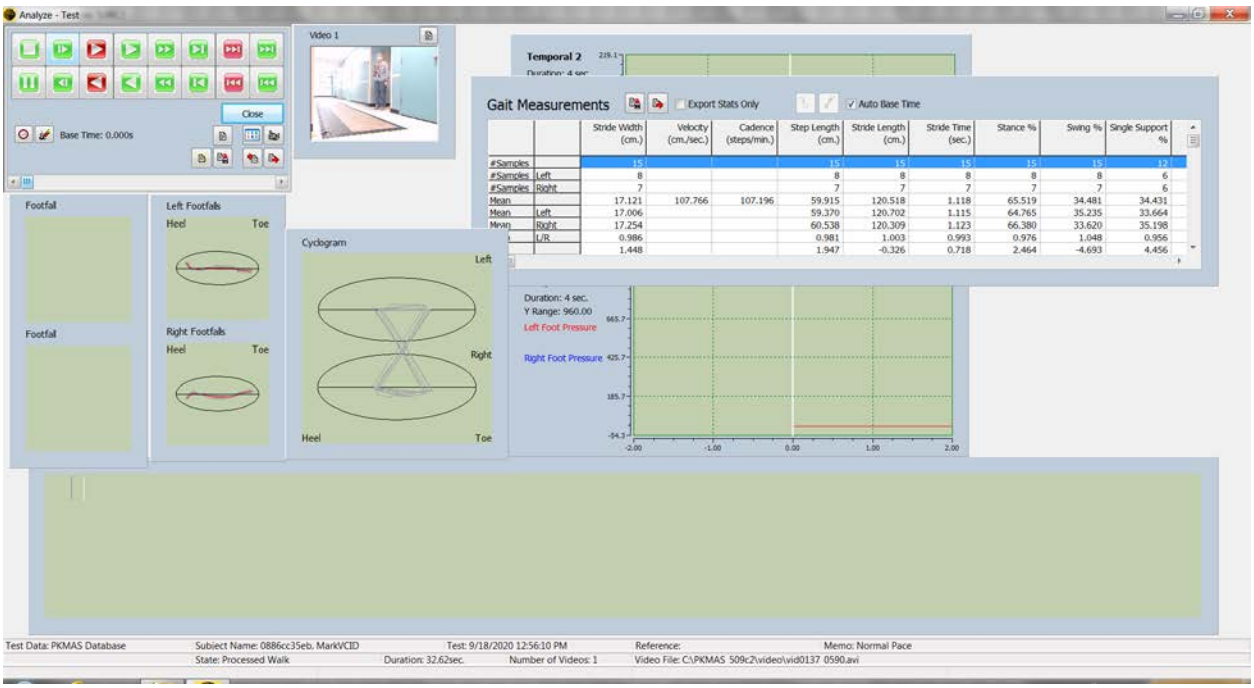
Saving Data

Part 1 – Saving Excel data file

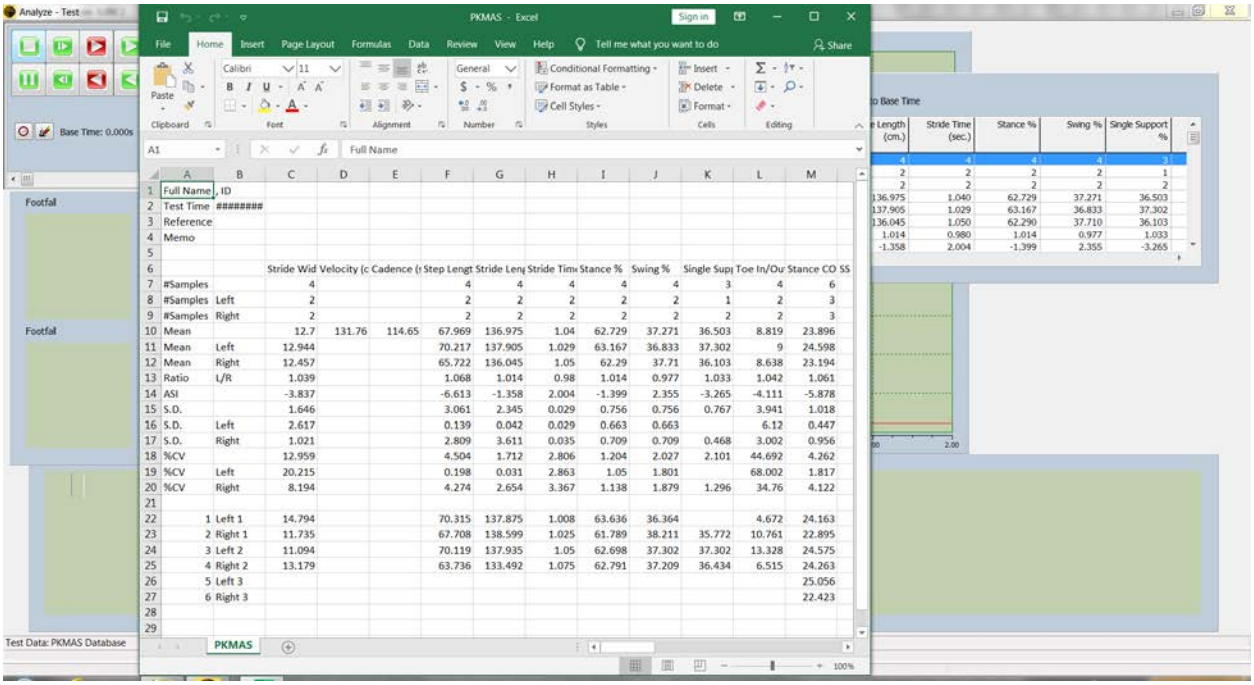
1. Select test you want to save and open



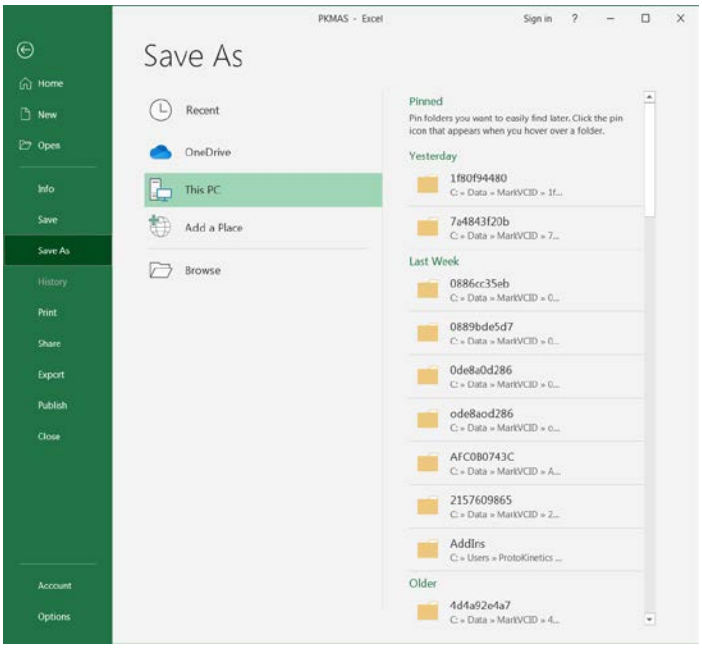
2. Click on Analyze test, screen opens



3. Click on Gait measurements – save as Excel button, Excel sheet with data opens

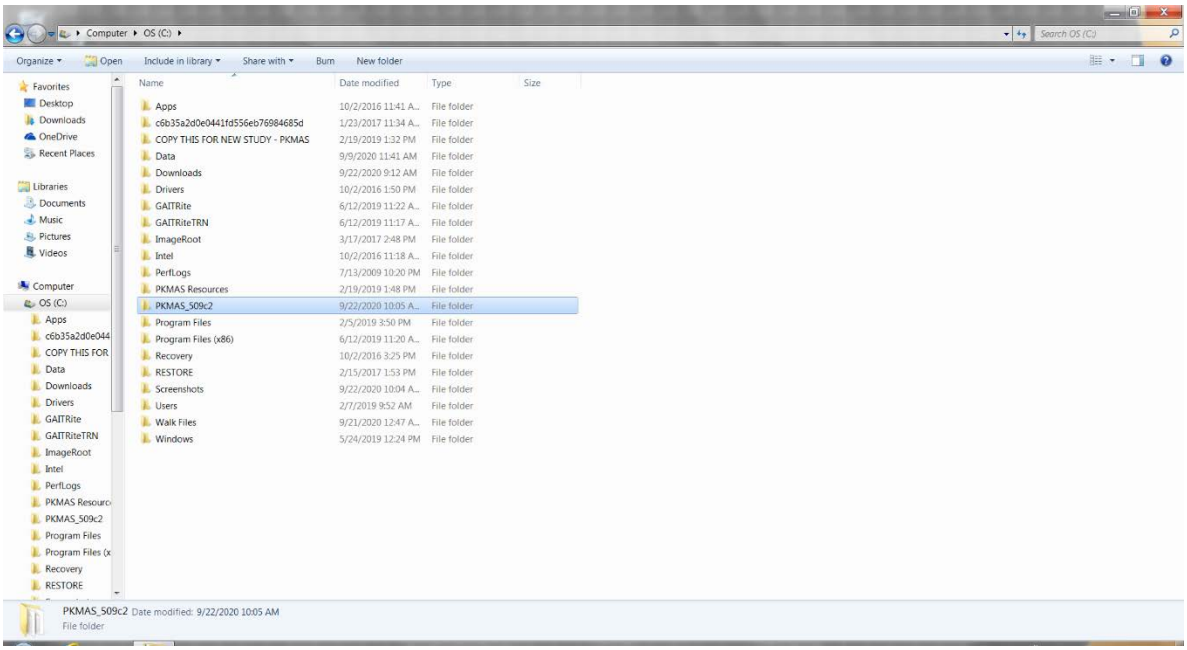


4.

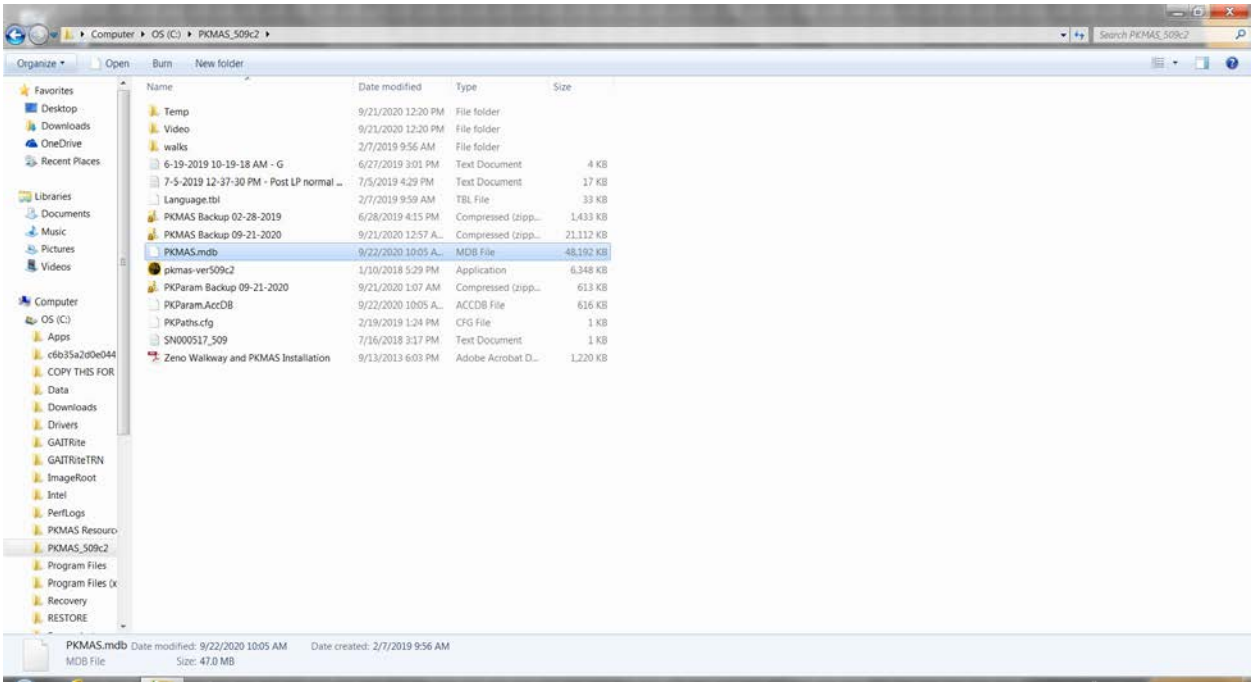


Part 2 - Saving Walk files

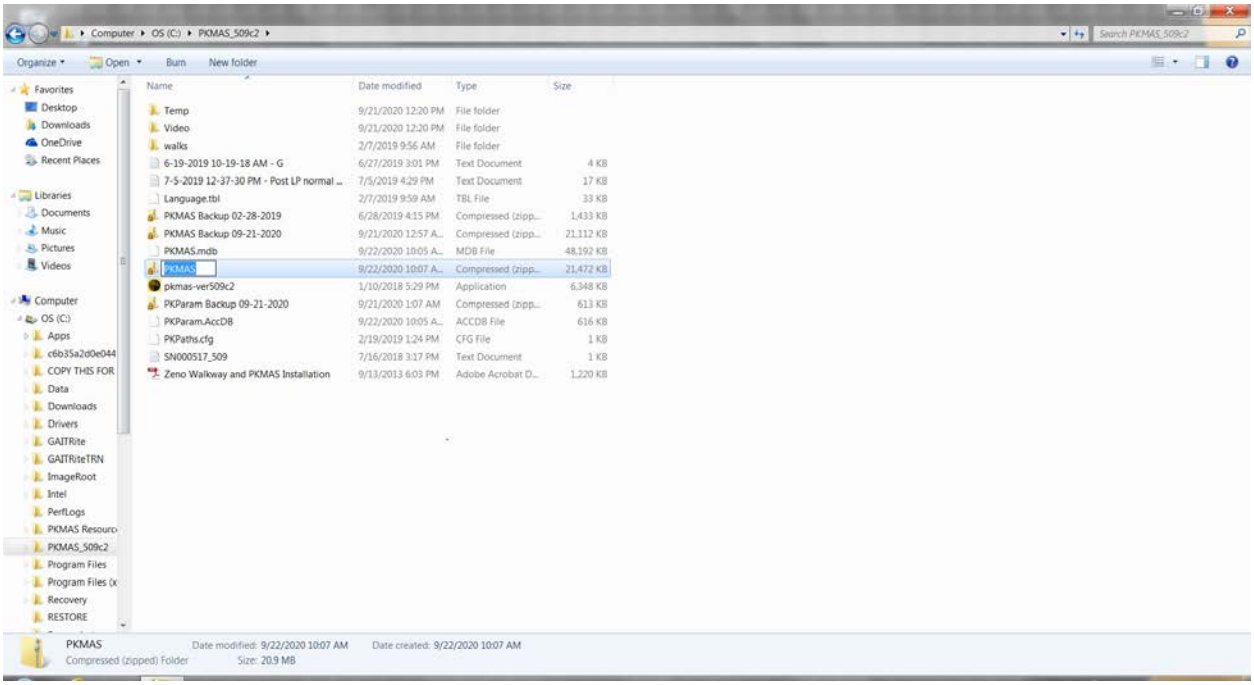
1. PKMAS folder



2. mdb file – right click, save as zip file



3. Rename with date



FRAMINGHAM HEART STUDY

High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT) Bone Study

MANUAL OF PROCEDURES

Offspring Exam 10/ Omni1 Exam 5

Table of Contents

1. Study Personnel

NAME	ROLE	INSTITUTION	E-MAIL
Elizabeth (Lisa) J. Samelson, PhD	Principal Investigator	Hebrew SeniorLife Institute for Aging Research, Boston, MA	[redacted]
Danette Carroll	Project Director/ Bone Technologist	Hebrew SeniorLife Institute for Aging Research, Boston, MA Framingham Heart Study- Perini Building, Framingham, MA	[redacted]
Douglas P. Kiel, MD, MPH	Co-Investigator	Hebrew SeniorLife Institute for Aging Research, Boston, MA	[redacted]
Mary L. Bouxsein, PhD	Co-Investigator	Beth Israel Deaconess Medical Center, Boston, MA	[redacted]
Gary Mitchell, MD	Co-Investigator	Mitchell Engineering, Inc. Norwood, MA	[redacted]
Ching-Ti Liu, MD	Co-Investigator	Boston University School of Public Health, Boston, MA	[redacted]
Steven Boyd, PhD	Co-Investigator	McCaig Institute for Bone and Joint Health, University of Calgary, Calgary, Canada	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

2. Study Overview

The primary purpose of the Bone Study is to measure bone microarchitecture using high resolution peripheral quantitative computed tomography (HR-pQCT; XtremeCT II, SCANCO Medical AG, Brüttisellen, Switzerland) in participants attending Offspring Cohort Exam 10/ Omni1 Cohort Exam 5. The HR-pQCT scans the lower leg (tibia), as shown in the **picture** (right), and the lower arm (radius). HR-pQCT bone scanning was performed at the previous Offspring Cohort Exam 9/ Omni1 Cohort Exam 4 (2011-2014). The two scans together will be used to investigate longitudinal changes in bone microarchitecture.

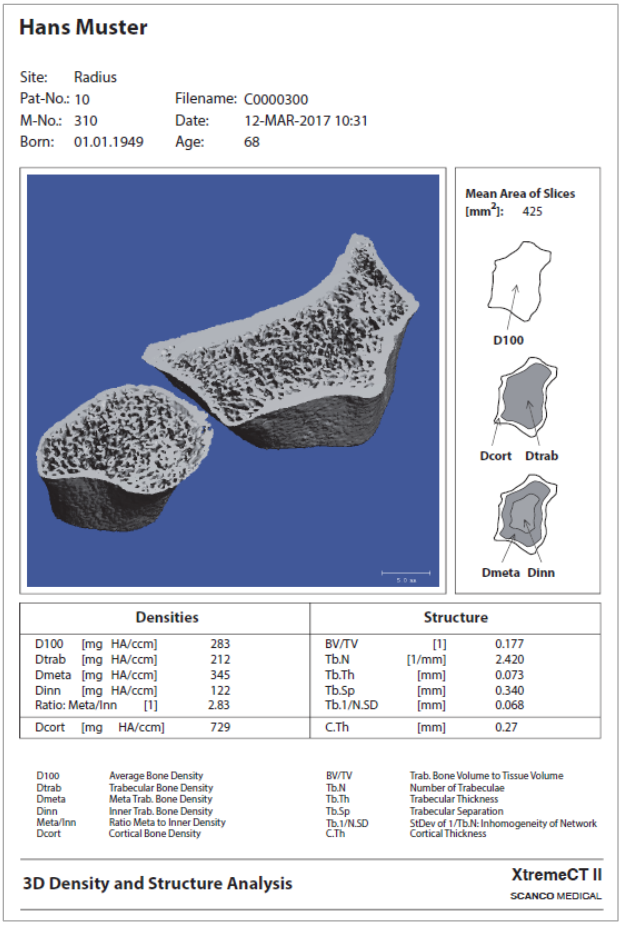
The time to complete the HR-pQCT bone testing is approximately 20 minutes. The procedures include:

1. Eligibility screening questionnaire
2. Scan of the right lower leg
3. Scan of the non-dominant forearm

An electronic data capture system (REDCap) will be used to record questionnaire data and information on scans completed.

HR-pQCT is a non-invasive method for measuring aspects of bone microarchitecture and strength. While bone mineral density measured via DXA is currently used as a clinical tool to diagnose osteoporosis and assess fracture risk, it is limited in its ability to describe additional characteristics that are important determinants of bone strength.

HR-pQCT provides precise measures of volumetric bone density, and also bone size, structure and microarchitecture. As shown in the **figure** (right), the output measures include 3D bone density and structural parameters separately for the cortical and trabecular bone compartment



This study will ascertain HR-pQCT measures in the Offspring/Omni1 cohort to determine how bone strength is affected by vascular dysfunction with aging.
Funding for this study is provided by the National Institutes of Health (R01 AG065299).

3. Training Components for Clinic and Backup Technologists

HR-pQCT exam components must be conducted by an ISCD-certified bone densitometry technologist (International Society for Clinical Densitometry), or a certified radiology technologist.

All personnel conducting the visit will be thoroughly trained in all clinic visit procedures, and an observational QA visit will be completed and recorded by other Bone Study staff once a year.

The backup technologist will do a hands-on review of clinic procedures once a month, including conducting a visit, to maintain competency.

Training for secondary backup when needed

Technologist will train and, as needed, review all clinic procedures with backup technologists. The backup technologists will complete all procedures, including:

- Daily clinic set-up and end of day procedures.
- Daily HR-pQCT QC1 phantoms, printouts, reference ranges, and weekly QC2 phantom.
- Procedures to follow if daily HR-pQCT QC1 or weekly QC2 reference ranges are outside acceptable range.
- Hands-on review of HR-pQCT ID conventions, exam logs, dealing with human subjects in research setting.
- Review of all HR-pQCT scanning protocols; review questions with participants regarding experience of nuclear medicine scans in the previous 7 days, previous fractures or replacements at scanning sites
- Review of HR-pQCT repeat scan protocol.
- Review of data collection via iPad Air and REDCap system.
- HR-pQCT positioning; how to determine if a scan is acceptable or requires a repeat; primary technologist will assess the backup technologist's HR-pQCT training scans to confirm competency.
- The Clinic Technologist will supervise the secondary backup technologist in conducting several visits with participants and conduct an observational QA review of one visit to confirm competency of the secondary backup, using the "Clinic Technologist QA Report and Summary".
- List of resources if technical problems occur: Dani Carroll (Project Director/Bone Technologist), Lisa Samelson (Principal Investigator), Douglas Kiel (Co-Investigator), Scanco Support, FHS IT. Examples include: FHS power

outage or network issues, unexpected 30-minute X-ray tube warmup, QC values out of range, REDCap unavailable.

Technologist QA Report

Framingham Bone Study

Offspring Exam 10/OMNI1 Exam 5

Summary QA Report

Name _____ Date_____

Observing (Name) _____ Number Participants Observed_____

1. Study Procedures

2. Study Time

3. Study Flow

4. Communication

5. Additional

QA Report

Time: Starting Time Ending Time:

1. Pre-visit preparation

2. Greeting Participant

3. Ask pre-HR-pQCT scanning questions –dominant side

4. Measure and record leg and forearm limb lengths

5. Leg/tibia HR-pQCT

   Directions about chair/leg positioning

   Scout view and set landmark

   Leg scan performed

   Fill out logbook

   Enter information into Redcap (id, samp #, meas #)

6. Forearm/radius HR-pQCT

   Directions about chair/forearm positioning

   Scout view and set landmark

   Forearm scan performed

   Fill out logbook

   Enter information into Redcap

7. Exiting procedures

4. Participant Selection for Bone Testing

All Offspring/Omni1 participants are eligible for Bone testing, although participants in the following categories would not be able to have a scan on the date of the visit:

a) Cognitively impaired participants will not be allowed to participate in the study unless they have a proxy who provides informed consent.

b) Participants who had a nuclear medicine scan done in the 7 days prior to their visit as radioactive tracers could affect bone density results.

c) Participants whose weight exceeds 330 lbs cannot have HR-pQCT assessments.

d) Participants who are unable to hold the arm or leg still for two minutes will not be eligible for the HR-pQCT scans, as motion may cause an inaccurate measure.

5. Bone Protocol Summary

This section provides a summary of the protocol. Detailed step-by-step instructions for specific procedures are provided in later sections.

- Eligibility screening: technologist will ask questions to determine eligibility, appropriate side of scanning and enter data into REDCap (3 minutes).
- HR-pQCT scanning: measures bone microarchitecture indices of bone strength. Participants will be seated in the special chair and must hold still during the scanning process. For tibia, the technologist will place leg in boot and insert into HR machine, scan will take 2minutes. For forearm, the technologist will place arm in manufacturer’s casing and insert into HR machine, scan will take 2 minutes.

6. Equipment

A. Technical Support Contact Information

Scanco Medical XtremeCT2 Scanner and Workstation

For all HR-pQCT operational or applications support, [redacted]

[redacted]

REDCap

REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. For REDCap support, email:

[redacted]

Personal Computer (PC)

The bone study technologist's PC is owned by HSL and is serviced by HSL's IT Department. The first point of contact for technical problems should be with HSL IT:

[redacted]

FHS IT Contacts:

[redacted]

B. Radiation Safety Registration and Supply List

[redacted]

th[redacted]

7. Quality Assurance Procedures (QA) for HR-pQCT

Important: a) The HR-pQCT machine (XtremeCT2 scanner) needs to remain powered on Monday through Friday at all times to help prolong the life of the x-ray tube. The

HR-pQCT PC workstation remains powered on, even over the weekends.

b) The HR-pQCT XtremeCT2 scanner has its own power on/off switch. The scanner is powered OFF at the end of day on FRIDAYS ONLY for the weekend, and

powered on again on Monday mornings. A key on the front side of the scanner is used to power on and off. NOTE: On Monday mornings, the technologist must

plan for a 30-minute warmup period for the x-ray tube before any QC or participant scanning can be done.

A. Daily QC1 for HR-pQCT

Each HR-pQCT system is delivered with a manufacturer's Phantom, which is used to check the functionality and the stability of the system. The phantom is divided into two sections. One section is optimized for testing the stability of the density measurement and the other for the stability of the architectural parameters. For scanning the two sections, a corresponding, locked control file is provided for each of them: 1. QC1 (performed daily) 2. QC2 (performed weekly)

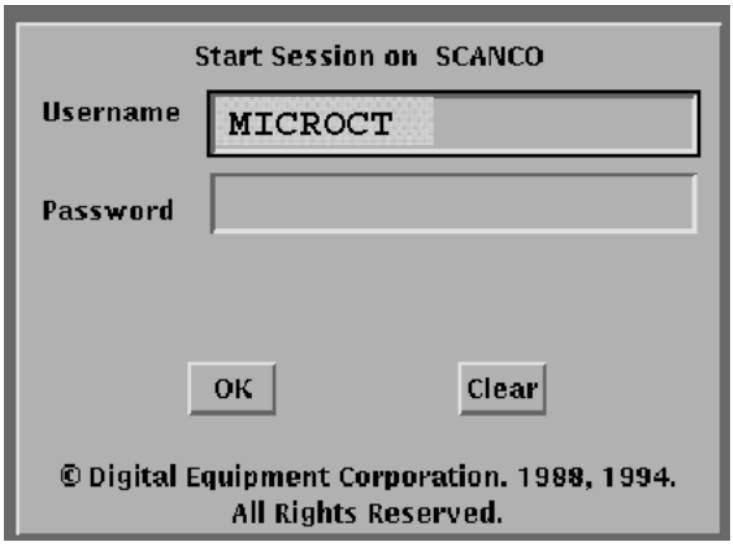
The evaluation of the phantom measurements is automated.

Image Phantom

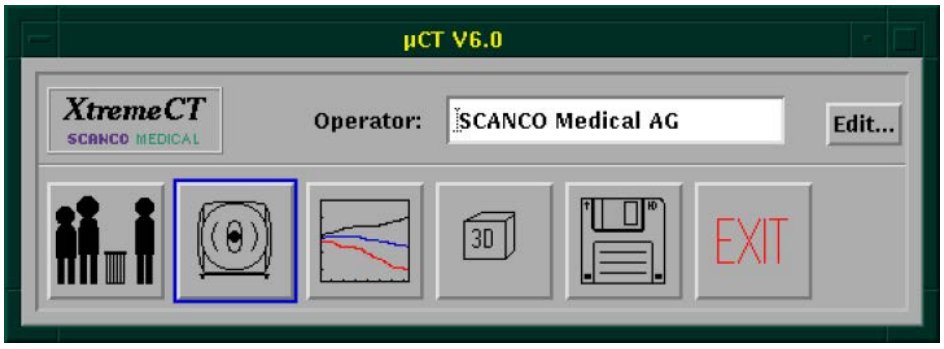
QC1 Daily Phantom to monitor stability of density measures:

It is very important to run the daily phantom measurement prior to the first measurement of a participant every day and make sure that the MEAN 5 value is within the +/- 8 mgHA/ccm tolerance range that has been established for the system. Example: If Mean 5 value is calculated at 798, the tolerance range is between 790 - 806. If a phantom Mean 5 measurement is above or below the acceptable reference/tolerance range, the phantom measurement will be repeated, for a total of 3 phantoms. If the second phantom measurement is within tolerance range, scanning may commence. Statistically 95% of the daily QC1 measurements are expected to fall within the established tolerance range. It is also expected that there will be rare out of tolerance range fluctuations in the QC1 value. As long as a second QC1 value falls back within the tolerance range, scanning may commence and no further action is required. If, however, a third phantom measurement is still out of range, DO NOT SCAN a participant, but report by email to support@scanco.ch, as this may indicate that the density values of scans will be inaccurate. Environmental factors, such as temperature and humidity, can sometimes cause fluctuations.

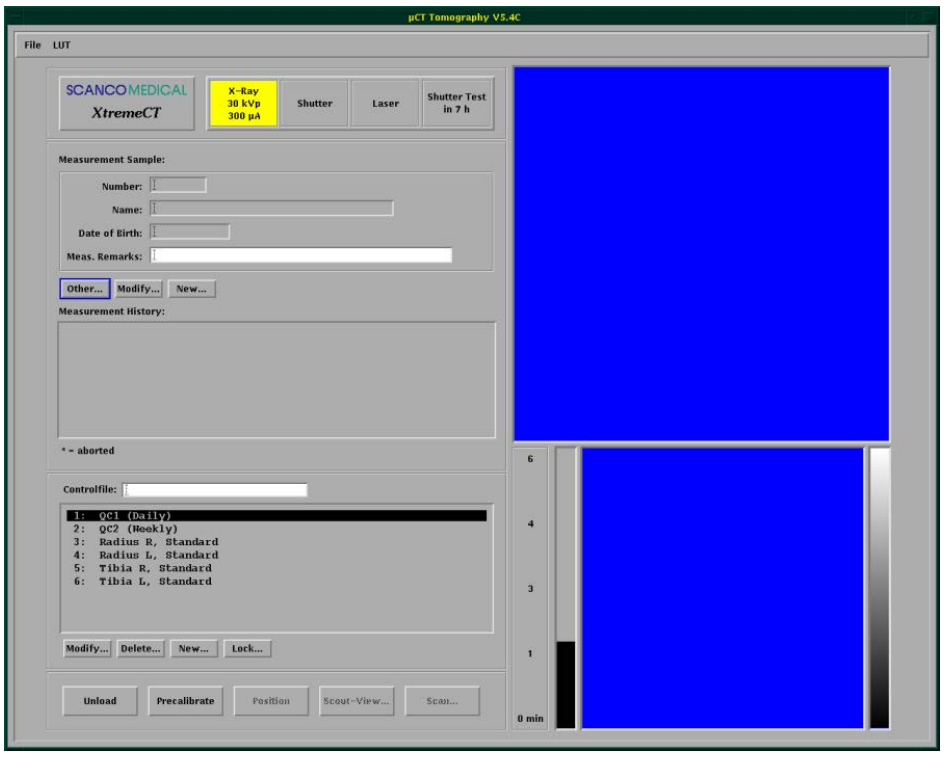
1. Move the mouse to wake up the system and log in with username and password, click OK or enter.



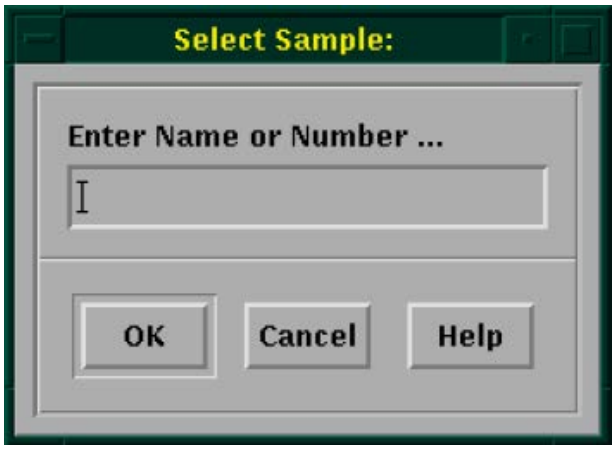
2. Click on "Scanner" icon at bottom left of screen (box second from left)



3. The main window of the measurement program will appear. Wait about 30 seconds for the input window to appear.



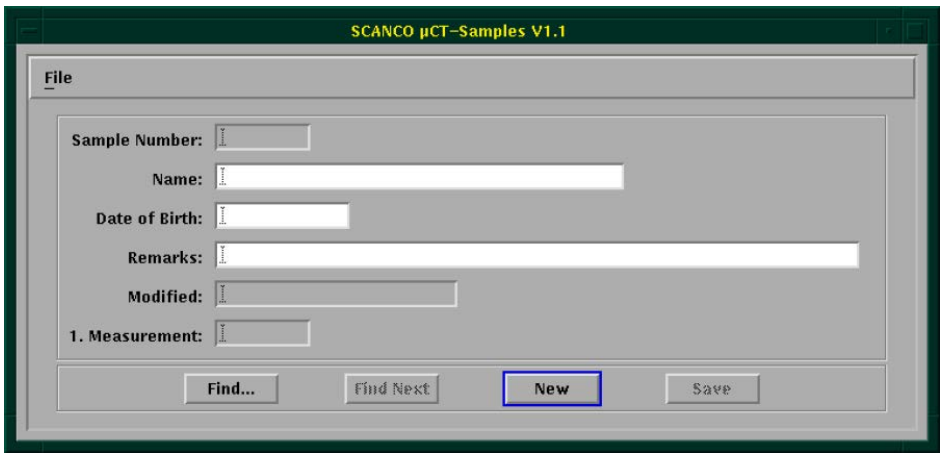
4. Enter ID number as 1 in the box under "Enter name or number". No names or other identifiers are entered. Click "OK".



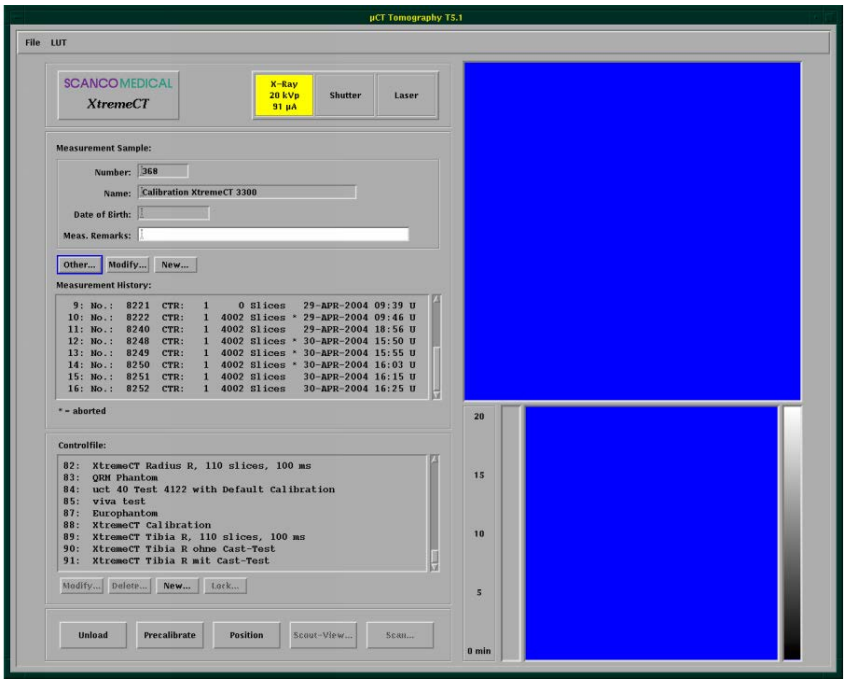
Click "Yes" in next box that states: "Sample name or number not found. Enter?"

In new window/input box, enter ID number again as 1 in the "Name" field. No other identifiers are entered. Click "Save".

In the upper left hand corner within the input box (not at extreme top left of screen), click on "File", Click on "Exit".



5. At Main Measurement screen, select **"QC1"** in box at bottom left under control file for the ***"daily"*** phantom measurement.



6. Insert the phantom if not already inserted. Note: Standard procedure is to insert the phantom at the end of the day so it will be in place for the next day's first step, the daily QC measurement.

7. Check the proper positioning of the phantom.

8. Click on "Precalibrate", then "Start" to perform the c*alibration* for phantom measurement (1 minute). This is not yet the phantom measurement.

9. When calibration is completed, you have 15 minutes to begin the phantom measurement. Click "SCAN", then "START" to begin the phantom measurement.

10. To analyze, wait a few minutes for the slices to reconstruct/load. Then click on "Evaluation/analyze" icon, and select "1" for QC1 program and load the phantom measurement. Check that all slices/sections are available. Then start the evaluation; in a few moments, the results will be sent to the printer that is networked to the workstation. Compare the measurement with the current acceptable Mean 5 reference/tolerance range, and file the printout in the HR-pQCT QC binder.

QC1 Daily Phantom Reference Value and Tolerance Ranges

The reference value and tolerance ranges are calculated each time that the scanner is *recalibrated by Scanco Support due to:

a) maintenance, which could be at the annual preventive maintenance (PM) visit, or due to an unexpected problem (Example: x-ray tube replacement)

b) scheduled or unscheduled recalibrations to correct or prevent persistent drift in the average Mean 5 daily values

*The technologist will request that Scanco Support perform a preventive recalibration every 5 to 6 months. At 4.5 months following a recalibration, the technologist will carefully monitor the daily averages for stability, and report any concerns to Scanco and the bone team. Rationale: If the recalibration occurs while the QC1 daily Mean 5 values remain within the tolerance range, density measures of scans will be accurate. If QC1 daily Mean 5 values fall outside the tolerance range subtly over time, we will have to recalibrate, then restore to disk and reanalyze all scans that were acquired during that period. A drifting trend in the Mean 5 daily values, even if values are within the tolerance range, can signify that a recalibration may soon be needed. We choose to request the preventive recalibration, thus avoiding retrospective reanalysis of scans.

How to Calculate the Mean 5 Reference Value and Tolerance Range

*****to be added*****

QC1 Daily Phantom PLOT to monitor Mean 5 values over time

In addition to daily monitoring by the technologist, the daily Mean 5 values are tracked and monitored over time using a customized report log which the program analyst converts to a plot one a month. This monthly plot is reviewed by PI's at the Obesity and Bone Risk Factors Monthly Meeting to observe and curtail possible drifts in Mean 5 averages.

To obtain the customized report log of Mean 5 values in HR-pQCT: Open the DECTERM window and enter **command.**

Obtain the log at the Scanco interface on the DXA room PC in "Results" file. Use Sharefile to transfer the log to the program analyst who will convert the cumulative data to a plot (sample below). The program analyst posts the plot to the study dashboard for group access.

Add Sharefile transfer procedure, and sample of plot.

B. QC2 Weekly Phantom to monitor architectural parameters

Use the same procedure as with the QC1 daily phantom measurement but enter the ID Name or Number as 2. Select the **"QC2"** controlfile for the ***weekly*** phantom measurement. The QC2 scan and analysis is performed typically on Friday mornings following the QC1 scan and analysis.

The reconstruction of the QC2 measurement will take longer than that for the daily phantom measurement. Start the evaluation the same way as with the daily phantom

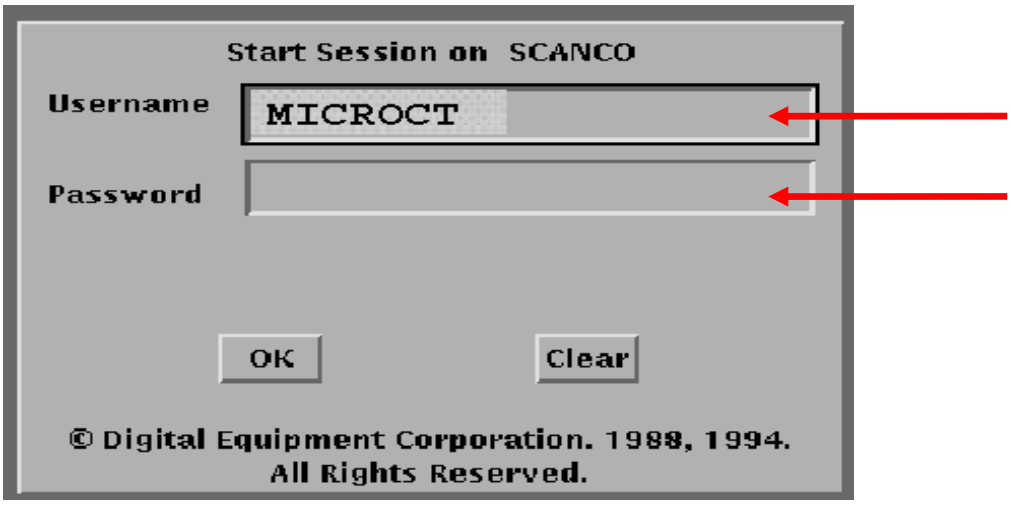
measurement, but wait about 30 minutes for the QC2 image slices to construct. Click on "Evaluation/analyze" icon, and select "2" for QC2 program and to load the phantom measurement. Check that all slices/sections are available. Start the evaluation. In a few moments, the results will be sent to the printer that is networked to the workstation. Compare the measurement with the current acceptable Rod Volume reference/tolerance range, and file the printout in the HR-pQCT QC binder.

If a QC2 phantom measurement is above or below the acceptable reference range, the phantom measurement will be repeated, for a total of 3 phantoms. If the third phantom measurement is still out of range, DO NOT SCAN a participant, but report by email to support@scanco.ch.

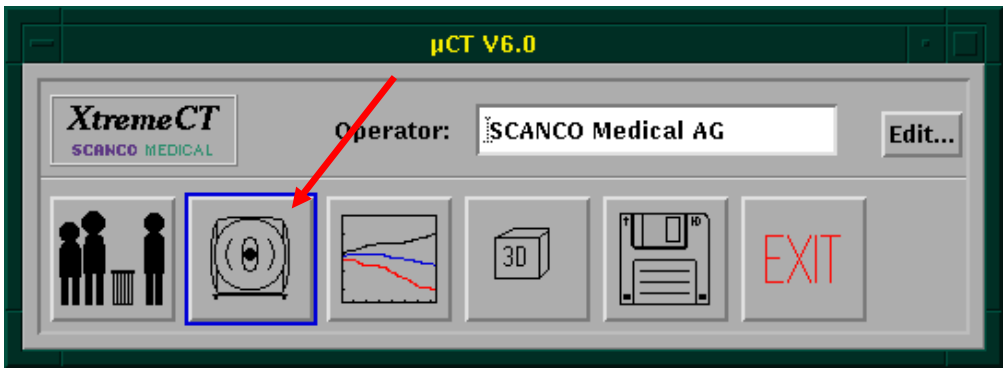
8. Pre-HR-pQCT Testing Procedures

Before participant enters clinic, the technologist will:

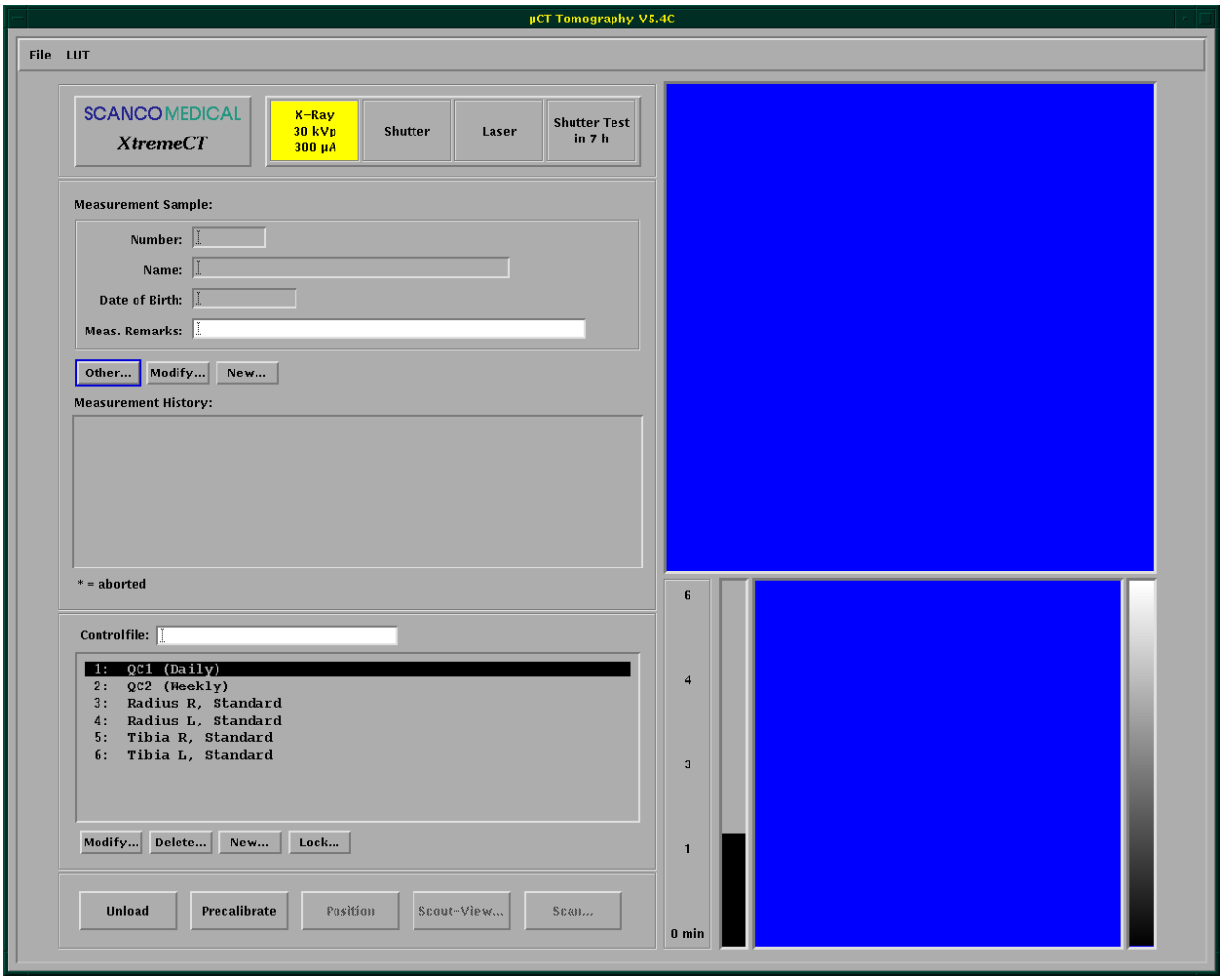
a) Drag mouse at HR-pQCT workstation to wake up the screen
b) Type in username: microct
c) Type in password: made1in2ch, and enter or OK



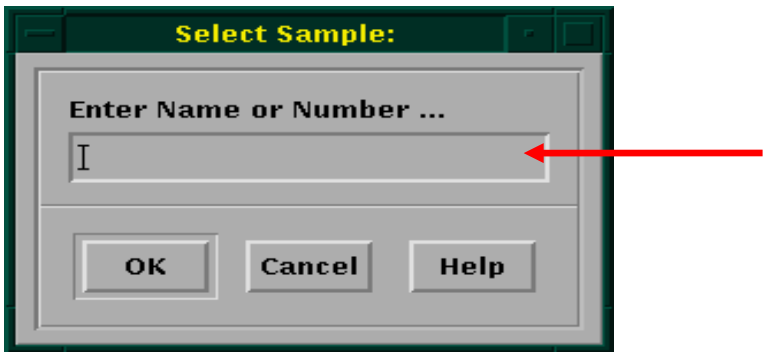
d) Box appears "File is not a Calendar data file"
e) Click OK
f) Enter Operator's assigned ID number at Operator field (operator's name should populate)
g) Click on “Scanner" icon at bottom left of screen (box second from left)



h) The main window of the measurement program will appear. Wait about 1 minute for the input window to appear.

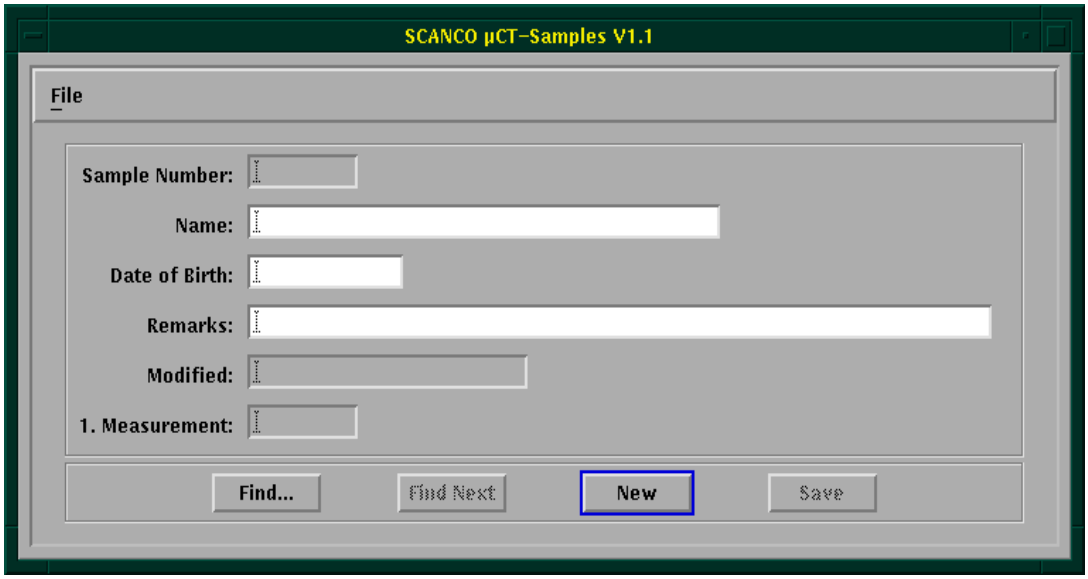


i) Enter participant FHS ID number carefully in the box under "Enter name or number". No names or other identifiers are entered.
j) Click "Ok"

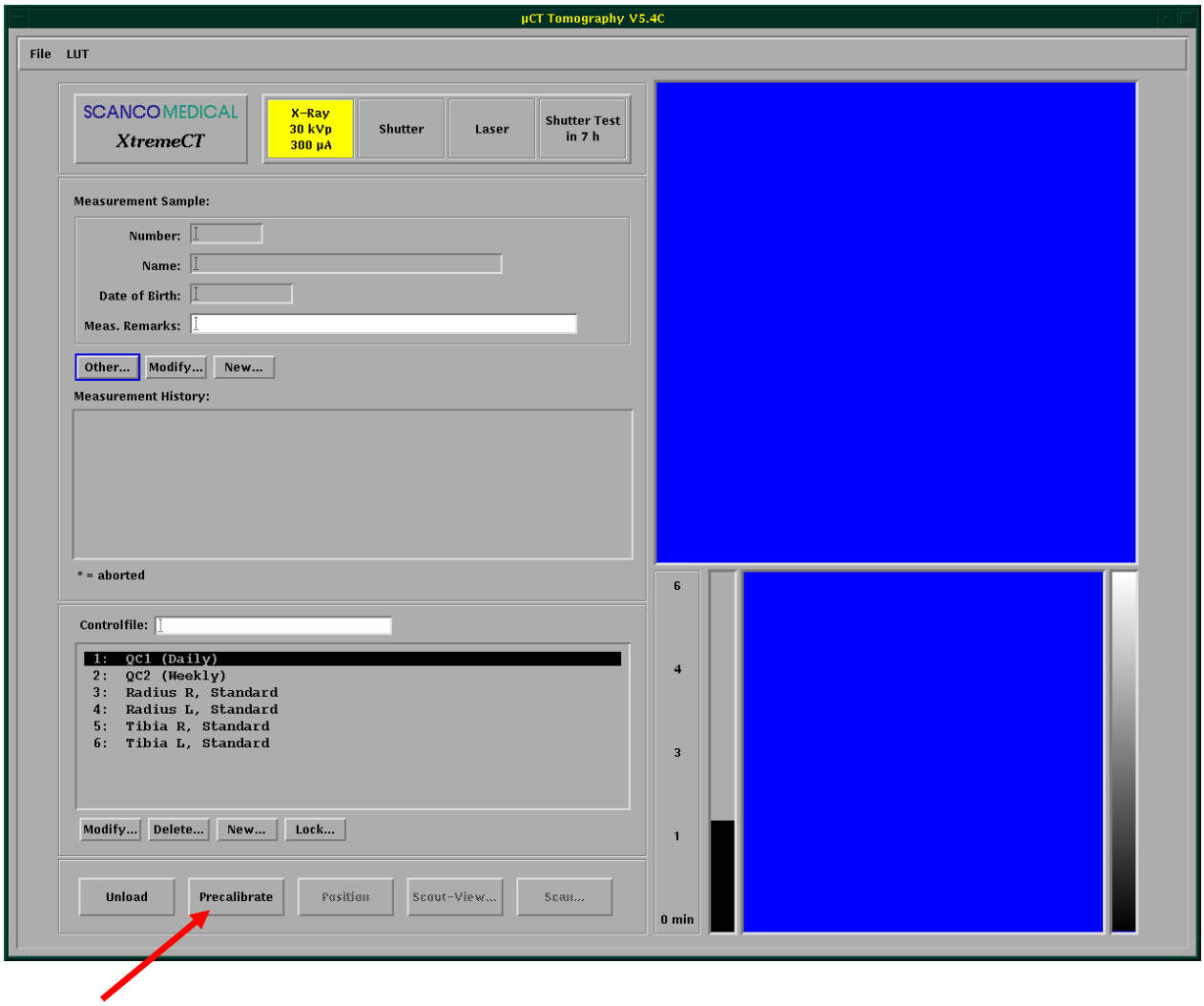


k) Click “Yes” in next box that states: “Sample name or number not found. Enter?”

l) In new window/input box, carefully enter participant FHS ID number again in the "Name” field. No other identifiers are entered.
m) Click “Save”
n) In the upper left hand corner within the input box (not at top left of screen), click on “File”, Click on “Exit”. Save”



o) The window with a unique sample number (samp no) that is assigned by the system appears. The participant ID follows "Name". The participant record is now complete for opening and ready for scanning of participant.
p) Select the default right tibia (TR) site to scan once the participant has arrived
q) Click on “Precalibrate”
r) Click on “Start Calibration". Precalibration takes about 1 minute so it can be run while the technologist either measures the limb lengths or positions the participant for the first scan. If the technologist determines that the left tibia will be scanned, and not the right, he/she will select the correct site before scanning.


µCT Tomography V5.4C
File LUT
SCANCO MEDICAL
XtremeCT
X-Ray
30 kVp
300 µA
Shutter
Laser
Shutter Test
in 7 h
Measurement Sample:
Number:
Name:
Date of Birth:
Meas. Remarks:
Other...
Modify...
New...
Measurement History:
* = aborted
Controlfile:
1: QC1 (Daily)
2: QC2 (Weekly)
3: Radius R, Standard
4: Radius L, Standard
5: Tibia R, Standard
6: Tibia L, Standard
Modify...
Delete...
New...
Lock...
Unload
Precalibrate
Position
Scout-View...
Scan...
6
4
3
1
0 min

9. Participant Testing Procedures

Receive Research Center visit schedule from FHS staff

A. Eligibility Screening

Greet participant in research center waiting area

No Offspring/Omni1 study participants will be excluded, although participants in the following categories would not be able to have a scan on the day of the visit:

1. Cognitively impaired participants will not be allowed to participate in the study unless they have a proxy who provides informed consent.
2. Participants who had a nuclear medicine scan done in the 7 days prior to their visit as radioactive tracers could affect bone density results.
3. Participants whose weight exceeds 330 lbs cannot have HR-pQCT assessments
4. Participants who are unable to hold their arm or leg still for two minutes will not be eligible for the HR-pQCT scans, as motion may cause an inaccurate measure.

B. Identify Sites to Scan

Once the participant has consented to complete the skeletal assessment, the technologist must identify which sites to scan using HR-pQCT per the protocol. The Bone Study Offspring Exam 10/Omni1 Exam 5 Questionnaire will be completed in the REDCap database in real-time using the iPad Air. The technologist will ask the following questions about the participant's previous fractures and dominant/non-dominant side. The information entered on the "Scan Info" page in REDCap will define which body sites to scan. See REDCap Scan Info page below.

To determine HR-pQCT scan sites:

1. **For the majority of activities (not just writing), which hand is used?**The opposite side is considered non-dominant, and is the correct side to scan.
   If the participant responds that he/she is ambidextrous, and considers neither side as dominant, the left forearm/radius will be scanned.

2. Have you ever fractured either forearm? If no, the non-dominant forearm will be scanned.
   If yes, the opposite forearm from the fractured forearm will be scanned.
   If yes and both forearms were ever fractured scan the forearm with the oldest fracture that is without metal artifacts.

3. Have you had a knee replacement, or ever fractured either ankle?
   If yes to knee replacement, the participant's comfort level will decide which leg to scan, but the right leg is always preferred.
   If yes and both knees were replaced, the right leg is preferred and participant's comfort level will decide.
   If yes to fractured ankle, the opposite leg will be scanned.
   If yes and both ankles were fractured, scan the leg with the oldest fracture that is without metal artifacts.

The following is the Bone Study Offspring Exam 10/Omni1 Exam 5 Questionnaire "Scan Info" page which is the model for the REDCap data entry system. In the event that REDCap is unavailable due to technical problems, the hard copy questionnaire will be used to record the scanning procedures and then the visit data will be entered into REDCap within 24 hours of its availability. The REDCap entries will be verified by the project director and bone technologist.

C. Questionnaire: HR-pQCT Scan Side and Other Scan Information

Determine HR-pQCT Forearm Scan Side

1. For majority of activities (not just writing), which hand is used?

|___| [1] Right [2] Left [3] Equal

2. Have you ever fractured your non-dominant forearm?

|___| [0] No [1] Yes

- If YES: Have you ever fractured your dominant forearm?
  [___] [0] No [1] Yes
- If YES: Scan the forearm with the oldest fracture
  [___] [1] Right [2] Left

  If NO: Scan dominant forearm

  [___] [1] Right [2] Left

If NO, scan the non dominant side

[___] [1] Right [2] Left (If equal, scan left forearm)

Determine HR-pQCT Leg Scan Side

3. Have you ever had an ankle fracture or knee replacement?

[___] [0] No [1] Yes

- If YES, check any that apply and scan the opposite leg
  [___] [1] Right ankle fractured[___] [2] Right knee replaced

  [___] [3] Left ankle fractured

[___] [4] Left knee replaced

- If both ankles were fractured, scan the leg with the oldest fracture

  [___] [1] Right [2] Left

- If both knees were replaced, scan the leg side based on participant's comfort

[___] [1] Right [2] Left

If NO, scan the right leg

HR-pQCT Information

5. HR-pQCT Sample Number (S-No.) |___|___|___|___| (if no scan done, enter [0])

(2z) Forearm side to scan (based on answers in Steps 1 and 2)

[___] [1] Right [2] Left

6. Is forearm scanned?

[___] [0] No [1] Yes

- If YES, is preferred forearm scanned (based on answers in Steps 1 and 2)
- If YES, proceed to enter scan measurement number
- If NO, select the reason:

  [___] [1] Cast/bracelet [3] Metal in forearm [5] Other

  [2] Tremor [4] Pain in shoulder

If NO, and neither forearm is scanned, select the reason;

[___] [1] XXXXXX
[2] XXXXXX
[3] Metal in forearm
[4] Exceed size limit
[5] Tremor
[6] Refused (specify): _____
[7] Other (specify): _____
[8] Coughing
[9] Parkinson's
[10] Peripheral neuropathy
[11] Pain

1st forearm measurement number (M-No.)

|___|___|___|___|

Is 1st forearm scan acceptable?

|___| [0] No [1] Yes

- If YES, proceed to Step 7
- If NO, proceed to Step 7 to acquire leg scan

HR-pQCT Leg Scan Information

(3z) Leg side to scan (based on answers in Step 3)

[___] [1] Right [2] Left

7. Is preferred leg scanned?

[___] [0] No [1] Yes

- If YES, is preferred leg scanned (based on answers in Step 3)
- If YES, proceed to enter scan measurement number
- If NO, select the reason:

  [___] [1] Metal artifact

  [___] [2] Other _____

If NO, and neither leg is scanned, select the reason:

[___] [1] XXXXXX
[2] XXXXXX
[3] Metal in forearm
[4] Exceed size limit
[5] Tremor
[6] Refused (specify): _____
[7] Other (specify): _____
[8] Coughing
[9] Parkinson's
[10] Peripheral neuropathy
[11] Pain

1st leg measurement number (M-No.)

|___|___|___|___|

Is 1st leg scan acceptable?

|___| [0] No [1] Yes

- If YES, proceed to Step 8
- If NO, request a repeat leg scan

Leg scan repeated?

|___| [0] No [1] Yes

- If YES, enter 2nd measurement number
- If NO, proceed to Step 8

If repeated, 2nd leg measurement number (M-No.)

|___|___|___|___|

8. If 1st forearm scan is not acceptable, is forearm scan repeated?

[___] [0] No [1] Yes

- If YES, enter 2nd measurement number
- If NO, proceed to Step 9

If repeated, 2nd forearm measurement number (M-No.)

|___|___|___|___|

D. Do Not Scan Procedures

Prior to HR-pQCT scanning, the technologist will ask all participants if they have had a nuclear medicine scan within 7 days of their clinic visit. If they have, the HR-pQCT scanning components of the visit will have to be rescheduled, if participant is willing, after an 8-day window has elapsed. Nuclear medicine scans are used for a variety of purposes including diagnosing metastatic cancer, and can affect the bone density results.

Some participants may have to be excluded from HR-pQCT scanning due to physical challenges which will most likely result in unevaluable scans due to movement. The technologist will not expose the participant to radiation, however minimal, if she is unlikely to acquire an acceptable scan. In the event of any of the following conditions, the technologist will not attempt to acquire HR-QCT scans:

1. Coughing spasms affecting the whole body that cannot be controlled with water or cough drops;
2. Obvious tremors or twitching, affecting the whole body;
3. Participant demonstrates or reports a medical condition such as:
    a) Parkinson's Disease, where movement can likely occur at rest and arms are most likely to be involved;
    b) Peripheral neuropathy that causes arm or leg discomfort or restlessness
    c) Shoulder injury on the side to be scanned causing pain or discomfort
    d) Breast cancer or any other surgical or medical condition causing pain or discomfort when extending arm
    e) Other conditions affecting the participant's ability to keep the arm or leg still during the scanning procedure.

The technologist may scan only an arm, or only a leg, if she and the participant agree that motion will not be a factor at that body site.

E. Data Entry of Participant Information

Data enter participant ID information into the REDCap participant information page and HR-pQCT patient ID page. Note: It is more efficient to pre-populate the records in REDCap when the clinic schedule is busy. However, if the participant cancels or is a no show, the ID record will have to be deleted or changed per system parameters.

The following two (2) systems are used to record participant visit data:

1. HR-pQCT
2. REDCap

F. OP Questionnaire using REDCap

"Participant Info" is the first page of the **OP Questionnaire** on the REDCap electronic data capture system. The bone technologist logs into REDCap on the clinic iPad Air and enters the following information:

1. Framingham Heart Study (FHS) Participant ID Number - the system will give a warning if the ID entered is not a valid FHS ID number
2. The participant's cohort, i.e., Offspring, Omni 1
3. Double enters the FHS ID Number
4. Clinic exam date
5. Gender
6. Have you had a nuclear medicine exam in the last 7 days? Yes/No
7. Examiner's name
8. Complete
9. Save

G. Imaging Procedures – General Information

Order of HR-pQCT scan acquisition is: 1) Leg/tibia 2) Forearm/radius

NOTE: In the event that there is insufficient time to acquire both scanning sites, the priority is: 1) Right Leg HR-pQCT 2) Non-dominant Forearm HR-pQCT.

The "HR-pQCT Repeat Scan Protocol" will be followed if an HR-pQCT scan is unacceptable. One forearm scan may be repeated, and one leg scan may be repeated with the participant's permission.

Following FHS research center protocol, work with FHS staff to escort participant to the next phase of his/her clinic visit.

The technologist writes the following in the exam logbook: Participant ID's, machine-assigned unique ID's, scan site information, and any relevant information about the participant which may affect scan results. Examples: Certain medical conditions, age when a fracture occurred at a scan site, lack of mobility, obesity, repeating a scan. This additional background is very informative during quality assurance and data cleaning of all scans.

The exam **logbooks** also serve as a checklist for the technologist to complete all aspects of analysis and data backup of each scan.

H. HR-pQCT Scanning - Basic Steps

1. Enter 5-digit ID (ex: 12345 Offspring, 76789 Omni 1)
2. Click OK
3. Save? Click 'Yes'
4. At Name, enter 5-digit ID again
5. Click 'Save'
6. Click in the same box: FILE, EXIT (The participant sample number will appear at the left)
7. Select the site to scan (Left or Right Tibia, Left or Right Radius)
8. Measure leg and forearm limb length in mm (ex leg 300.0 mm, forearm 260.0)
9. Precalibrate before scanning (1 minutes)
10. Position participant for scan
11. Close door
12. Click 'Scout View'; use the sliding scale to bring the image up or down until the landmark is positioned to set the reference line.
13. Enter leg length or forearm length in the length fieldClick Reference Line and drag and drop reference line at target landmark on the image
14. Click "Save Scout"
15. Click "Scan"
16. When scan complete, review image to determine if acceptable; if not acceptable, ask permission to repeat. One repeat HR-pQCT scan of the leg and the forearm per visit is permissible, once participant agrees.
17. Try to complete HR-pQCT scanning session within the 15 minute precalibration window. Otherwise, you must precalibrate again and lose time.

I. PRE-HR-pQCT SCANNING PROCEDURES

Limb Measurements Protocol

Equipment required:
Cloth tape millimeter (mm) measure
Black, non-permanent fine-tipped marker

Tibia Length

1. The right leg is the preferred side to scan. Use the REDCap OP Questionnaire to ask the participant if they have ever fractured their right leg or ankle.
   If **yes** we will scan the left leg *without* history of fracture
   If **both** legs have history of fracture we will scan the leg with the **oldest fracture**
2. If possible, with the volunteer seated, have him/her sit so that the ankle of the leg to be scanned is resting on the knee of the other leg as if to make the shape of the number 4 (See Method 1 below). This will allow for more optimal measuring of the tibia. If this is not comfortable for the participant, alternate methods 2 or 3 can be used. **See Methods 2-3below)**.

Method 1: Demonstration of optimal method protocol for measuring tibia length. Note the skin marking at the distal extent of the medial malleolus and at the medial side of the tibial plateau.

Method 2: Ask subject to sit his/her ankle to be scanned on the opposite ankle.

Method 3: Ask participant to sit on the exam chair, and slightly open his/her leg, keeping the foot flat on the floor.

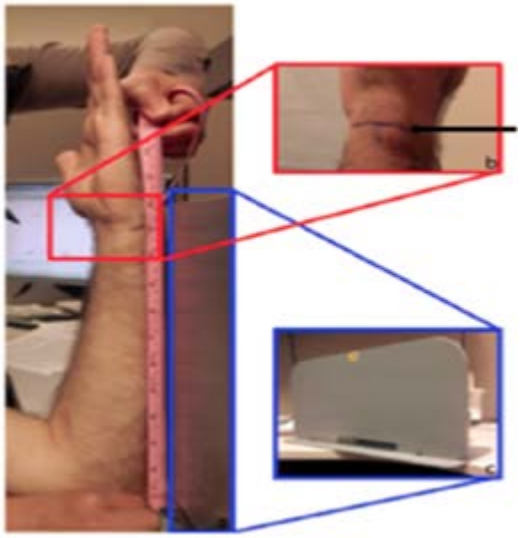
3. Once the leg is positioned comfortably to measure, palpate the medial malleolus (bump on the inside of the ankle) and draw a small mark at the distal extent of the medial malleolus. (As depicted in the 3 Methods above.)
4. Palpate below the medial side of the patella for the tibial plateau. This is the ridge/flat spot that is felt roughly 1 inch below the patella and is the most proximal part of the tibia. Mark this spot with the marker.
5. Run the tape measure from the mark near the medial malleolus to the tibial plateau mark, ensuring the tape measure is flat against the skin and reading metric.
6. Record the length of the tibia in millimeters (mm), e.g. **427.0**

Forearm Length

1. The non-dominant forearm is the preferred side to scan. Use the REDCap OP Questionnaire to ask the participant which is their dominant arm. Ask whether they have ever fractured either of their forearms.
   If **no fracture** we will measure and scan the non-dominant arm.
   If yes, there is a **prior fracture in the non-dominant arm**, we will **measure and scan the dominant arm.**
   If **both** arms have history of fracture, we will **measure and scan the arm with the oldest fracture**.
2. While seated in a chair, have the subject place their elbow on a hard surface (arm of chair) with the elbow bent to 90 degrees and the hand in the air.
3. Palpate the ulnar styloid (bone on the pinky side of the arm, proximal end) and make a mark at the mid-point of the ulnar styloid (**Figure 1 below**). It is easy to see the styloid if you have the subject flex and extend the wrist.

4. Run the tape measure from the table top to the mark, ensuring the tape measure is flat against the skin and reading metric.
5. Record the length of the radius in millimeters (mm), e.g. **255.0**

Figure 1. Demonstration of protocol for measuring forearm length. Note the skin marking at the midpoint of the ulnar styloid.



Forearm Cast - Air Pump Protocol

1. The air pump easily attaches to the side of the cast, where there is a white valve to attach to.
2. By pressing the pump, air is taken out of the cast so that it is able to conform to the participant's arm. Squeeze the pump 3-5 times.

3. The pump can then be detached from the cast, and the valve closed. Air will not leak out or in during this process.
4. After acquiring scan, let air back into the cast to prepare to conform to the next participant's forearm. Pull the red knob located on the white valve, being careful

that the knob doesn't go beyond the limit of the valve.

5. Press on the cushions to disperse the air inside. Once completed, push the red knob back down to stop air flow and close the valve.

J. HR-pQCT Tibia (Lower Leg)

Once the participant has answered the technologist's questions about his/her non-dominant side and fracture history, the technologist will:

1. Make sure that the participant is seated comfortably in the HR-pQCT chair, with the chair at its lowest position.

2. Ask the participant to remove the shoe and any ankle jewelry from the leg to be scanned.
3. Position the lower leg into the leg casing, with the foot resting all the way down into the casing/boot. Strap the leg into the casing at the foot and mid calf. The casing pad may be removed and replaced with a smaller or larger one to accommodate the participant's leg size, or removed entirely for a larger leg. The leg casing/boot also has different size insoles to accommodate the size of the foot.

Remind participant that their heel should be all the way back in the cast to prevent movement.

4. Instruct the participant to sit back in the chair while the height of the chair is adjusted. The chair will be raised by standing behind the chair and pumping the hydraulic pedal at the lower left side of chair. The participant's knee should be nearly level with the gantry opening. It typically takes 14 pumps on the pedal to reach the proper height.
5. Open the bore cover, lift the participant's leg and guide the casing into the casing slider. Position the casing into the bore while holding down the release/lock lever until the casing snaps into the locked position at the gantry. Check that the casing is securely locked into position. If not, repeat the steps until it is secure. Then slide the casing all the way into the bore and close the bore cover.
6. Once again, instruct the participant to sit back in the chair, reminding him/her to stay still and not to move at all during the 2-minute scan. Gently move the chair sideward or forward or backward slightly until the participant says they feel most comfortable. Make sure that their leg is straight, and they haven't entered HRp at an angle. Double check that the participants' knee is not bent, and if so adjust height accordingly. Provide participant with a foot stool for the leg not being scanned to prevent movement and maximize comfort so participant is ready and able to be still for the 2-minute scan.

7. To start the measurement, select the scan site which is right tibia (unless the fracture or knee history calls for the left tibia to be scanned).
8. Click "scout view".
9. Enter participant limb length in the length field in mm BEFORE starting Scout View. Click Start.
10. Use the sliding scale to bring the image up or down until the landmark is positioned to set the reference line.
11. Click on and drag reference line to the appropriate landmark in the tibia image; click “save scout”.
12. Click "scan" and "start". The scanner will flash progressive blue lights while it is in scan mode.
13. Review the leg/tibia image slice at the HR-pQCT computer to see if the scan is acceptable, or if there are motion artifacts (grade 4 or 5), which may make the scan unacceptable. If the scan has motion artifacts (grade 4 or 5) and cannot be used for evaluation, advise the participant that there was some involuntary movement and ask if he/she would consent to repeating the leg scan. The leg HR-pQCT measure is the most important one to acquire.
14. When leg scanning is complete, open the bore cover. To release the casing, raise the end of the casing a little bit and then gently slide it to its outer most position. The casing will still be in a locked position at the gantry. Hold down the release/lock lever and pull the casing out completely. Note: If the casing seems difficult to remove, have participant bend at the knee slightly.
15. Unstrap the leg casing and remove the participant's leg. Instruct the participant to stay seated, explaining that you must lower the chair before he/she gets out of the chair.
16. Press the hydraulic pedal to the floor to lower the chair to its lowest position.
17. Instruct the participant to stay in the chair for the forearm scan.

K. HR-pQCT Scan Acquisition – Radius (Forearm)

1. Make sure that the participant is seated comfortably in the HR-pQCT chair, with the chair at its lowest position to the floor.

2. On the forearm side that is to be scanned, lower the arm of the chair by raising the black toggle under the arm to release it and swing it backward, the arm of the chair must be out of the way to properly position the forearm for the scan.
3. Ask participant to remove bracelets and watches from the forearm that will be scanned and explain and demonstrate how the forearm will be placed in the manufacturer's casing. (Rings can be left on fingers.)
4. Explain that the scan will take about 2 minutes and it is imperative that the participant stay still and not move at all for 2 minutes. The scanner detects the slightest movement. If there is any movement, the scan may have to be repeated with the participant's permission.
5. Position the forearm to be scanned inside the manufacturer's casing, so that the forearm is resting comfortably from wrist to elbow and against the cast cushion, and the thumb and fingers are resting comfortably around the cast. Participant should have their forearm in straight, then turning their hand sideways to follow the cast, with their thumb on the outside, and fingertips resting or wrapped around top edge of cushion. There is both a left and right cast to use for forearm scans. Use the air pump to remove air inside the cushions and help cast conform to participant.
6. Instruct the participant to keep the hand and fingers relaxed. Participants with larger hands or a longer forearm may need to have their fingers higher up on the

cast, and wrapped around cushion.

7. Strap the forearm in the manufacturer's casing with the three velcro straps, paying close attention to the amount of room at the wrist and hand area. If the hand and forearm are not strapped snugly enough, this may cause movement during the scan.
8. Push the participant in the chair close to the scanner. Explain that you will first position the cast with forearm inside the scanner, and then maneuver the chair to the most comfortable position for the 2-minute scan (typically parallel to scanner).
9. Open the bore cover, and guide the manufacturer's casing into the casing slider, Position the manufacturer's casing into the bore while holding down the release/lock lever until the casing snaps into the locked position at the gantry. Check that the manufacturer's casing is securely locked into position. If not, repeat the steps until it is secure. Then slide the manufacturer's casing all the way into the bore and close the bore cover.
10. Encourage the participant to rest his/her head and shoulders back on the chair while moving the chair forward or backward slightly until the participant says they feel most comfortable and are ready and able to be still for the 2-minute

scan.

11. The above picture shows the correct placement of casing ready to lock.
12. Select scan site.
13. Enter the leg or forearm length in millimeters (mm) in length field BEFORE starting Scout View.
14. Click "scout view" and "start".
15. Click on and drag reference line to the appropriate landmark in the radius image. **NOTE: THIS IS THE MOST CRITICAL STEP IN THE SCANNING PROCEDURE SO CAREFULLY DECIDE ON PLACEMENT OF THE LINE!!**
16. Click "save scout" and then "ok."
17. Click "scan" and "start". The scanner will flash progressive blue lights while it is in scan mode.
18. Review the forearm/radius image slice at the HR-pQCT computer to see if the scan is acceptable, or if there are motion artifacts (grade 4 or 5), which may make the scan unacceptable. If the scan has motion artifacts (grade 4 or 5) and cannot be used for evaluation, advise the participant that there was some involuntary movement and ask if he/she would consent to repeating the forearm scan.
19. When forearm scanning is complete, open the bore cover. To release the manufacturer's casing, raise the end of the casing a little bit and then gently slide it to its outer most position. The casing will still be in a locked position at the gantry. Hold down the release/lock lever and pull the casing out completely.
20. Unstrap the arm casing and remove the participant's arm from casing. If scanning is complete, instruct him/her to get up and out of the chair, put on shoe and, if applicable, any arm jewelry that was removed.

NOTE: The technologist may need to read additional image slices to determine if a scan is acceptable. The system takes a few minutes after scanning to reconstruct all slices. After a few minutes, click on the "analyze" icon to view more image slices and determine if the forearm and/or leg measurements are acceptable.

L. Repeat HR-pQCT Scan Protocol

Acquisition of HR-pQCT leg and forearm scans are the highest imaging priority for the skeletal assessment. The technologist will make every effort to assess if a leg or forearm scan is acceptable for analysis. If a scan appears to be unevaluable, the technologist may repeat one leg scan and one forearm scan with the participant's permission. If either the leg or forearm repeat scan still has motion artifacts and is unacceptable for analysis, do not scan. Only one repeat scan of each limb is permissible. The technologist will:

- Always check the first image slice that appears at the HR-pQCT screen when the leg or forearm scan is completed since motion artifacts may be seen on the first slice if there are any. If the scan is unevaluable for bone architecture measure based on the first slice, i.e., the movement artifact grade is a "4" or "5", the technologist will continue with visit procedures, following the "Imaging Priority Protocol". If more image slices must be viewed to determine whether the scan is acceptable or not, the technologist will continue with visit procedures. Then when the machine has loaded more image slices, she will click on the analysis icon for the scan to view more slices, and determine if the scan is evaluable or not.

- If a leg or forearm scan is not evaluable (movement artifact grade is a "4" or "5"), the technologist explains to the participant that there may have been some involuntary movement causing the scan to be unusable, and asks permission to repeat it. If participant agrees, re-position and acquire the second scan.

NOTE: If time is short and it is clear that there are motion artifacts, follow the "Imaging Priority Protocol" to acquire an acceptable scan within the time constraints of the visit. This may mean that some lower priority procedures will not be performed.

First imaging priority: HR-pQCT LEG scan

Second imaging priority: HR-pQCT FOREARM scan

10. Post-HR-pQCT Scanning - Image Analysis

There are three forms of scan analysis performed on HR-pQCT radius and tibia scans. First, the trained technologist visually reviews the scan image slices to determine if the scan will yield acceptable measurements by rating the degree of movement detected in the image slices. The XtremeCT measurements can be affected by extremely slight movements, and a high degree of movement renders the scan unreliable for bone microarchitecture measure. Following Scanco's Guidelines for Motion Artifact Grades below, the technologist records the motion artifact grade in the HR-pQCT exam **logbook**, and also enters the grade in the **Bone Study Questionnaire CT Page on REDCap**. Each scan must be assigned a motion artifact grade in REDCap to identify it as: 1) an evaluable scan for bone microarchitecture; 2) an evaluable scan for volumetric BMD; 3) an unacceptable scan for any measure.

A. Motion Artifact Grading

The following is the motion artifact grading system that is applied to each scan.

1) Grade 1 = No movement (highly acceptable)
2) Grade 2 = Slight movement (very acceptable)
3) Grade 3 = Some movement (acceptable)
4) Grade 4 = Moderate movement, acceptable for some measures
5) Grade 5 = Severe movement (unacceptable)

B. Standard Analysis (Note that there is no Extended Cortical Analysis on XtremeCT 2 scans. This is now part of the standard analysis.)

We will analyze scans according to the manufacturer's recommendations (see SCANCO ExtremeCT II manual), and the following customized addendum provided by N***icolas Vilayphiou and Mary Bouxsein (2016).***

The following steps are to be completed only after the scan has fully reconstructed. Full scan reconstruction will include 61um, 168 slices. You can check the status of the reconstruction in the terminal window by typing “show que”.

- Start the task that automatically creates periosteal contours of the Radius or Tibia.
- Start the Evaluation Program
- Select scan to load (168 slices)
- Click “T…” to open the 3D Evaluation dialog box
- Click “Select” to select
- Script #3: XtremeCT II - Autocontour Largest bone (Radius or Tibia)
- Click “Submit Evaluation”

The job takes about 5-10 minutes per scan to execute.

One may submit several autocontouring jobs to the Evaluation queue, and they will be successively executed as background tasks. At completion of the job, a notice appears in the terminal.

The result of this task MUST be checked prior to submitting the actual evaluation task.

- Conduct visual check of the periosteal contours.
- Start the Evaluation Program
- Select scan to load (168 slices)
- The scan should be loaded automatically with the contour generated by the previous step
- If necessary, click the Load button in the middle of the Graphical Interface, to load all slices in the memory of the program (may take up to 30-60s).
- Zoom 3x on the bone of interest.
- Click the Right Arrow > button, to browse through slices and check on the position of the contour.
- Make corrections when needed, on individual slices, or on ranges of slices using Morph options (found in the dialog box related to C…
- If corrections were made, Click "File" à "Save GOBJ" to save modification.
- 3D Microarchitecture and Density Evaluation
- If no corrections were needed, one can proceed immediately to submitting the Evaluation task.
- Click "T…" to open the 3D Evaluation dialog box
- Script #10 for radius (or #11 for tibia) must come preselected, if not click "Select" to select
- Script #10: Radius 4% Patient Evaluation 61µm - GR=1
- Script #11: Tibia 7% Patient Evaluation 61µm - GR=1
- Click "Submit Evaluation"

Checking the 3D evaluation and trabecular contour

The user may want to correct the trabecular contours that were automatically generated during the analysis.

What follows is a complement to the standard analysis, used only if the operator deemed it necessary to make corrections to the contours of Trabecular bone.

- Start the Evaluation Program
- Select scan to load (168 slices)
- Zoom 3x on the bone of interest
- Load trabecular contour: Click "File" -> "Load GOBJ…"

- Select C000xxxx_TRAB_MASK.GOBJ in the coming dialog box
- Check the contour on all slices
- Perform manual corrections if needed, on individual slices or on ranges or slices using the Morph option
- Click “File” à “Save GOBJ” to save modifications if any.

If any corrections have been done:

- Click “T…” to open the 3D Evaluation dialog box
- Click “Select” to select

Script #13: Relative Sites Eval. 61um, After corr. on GOBJ - GR=1

- Click “Submit Evaluation”

If no corrections were made, either exit the program or load another scan to work with.

For scans with a motion artifact rating of 1, 2, 3 or 4, the standard analysis is performed as soon as possible following the scan acquisition.

C. Micro Finite Element Analysis (mFEA)

mFEA is conducted by our collaborator, Steven K. Boyd, PhD, University of Calgary at Alberta, Toronto, Canada. Scans to be included for mFEA analysis will have motion artifact grades of 1, 2 or 3, will be fully analyzed with scan results submitted via upat_list, and will be cleaned and reviewed for outliers. See "Transfer to University of Calgary - Micro Finite Element Analysis (mFEA)"

11. Data Procedures

A. Back-Up Procedures

Ultrium 0-4 1.6 TB Data Cartridges (One tape holds 400-450 XT2 scans)

The technologist will:

1. Use Data cartridge for daily backup of RAW data

2. Use Data cartridge for IMAGES to be backed up/moved to tape only after they are fully analyzed, data cleaned, and outliers reviewed by PIs. The tape is labeled with the date range when the scans were acquired
3. Use Data cartridge for Weekly backup of database (2 tapes: 1 marked Backup 1, and 1 marked Backup 2, used on alternate weeks to minimize risk of data loss)
4. Use Data cartridge for semi-annual backup of OPERATING SYSTEM (OS) to reduce time to reconstruct OS data if lost

The FIRST time a data cartridge is used, INITIALIZE to format the tape. Once data is mounted on the tape, NEVER INITIALIZE again or all data on the tape will be lost.

At the HR-pQCT Backup Program screen, it is important to understand how the backup functions work:

"MOVE TO"TAPE – deletes data from HR-pQCT computer hard disk. That data will exist only on the tape. Therefore, it is imperative to label the HR-pQCT Image Tape with the date range within which the scans were acquired. The date range for each image tape will be no more than one calendar year. The image can be moved from the tape back to the computer hard disk when needed. It is necessary to move images to tape to free up hard disk space. All scans reside on hard disk 2 (DK2).

"COPY TO" TAPE - leaves the data on the HR-pQCT computer hard disk, and copies data and/or images to tape.

"COPY TO" DISK - Once images have been moved to tape, they can be *copied* back to hard disk (DK2) to temporarily review the images onscreen. However, this can take a significant amount of time as the system needs to search the tape for the selected scans and then reconstruct all 110 image slices per scan back to hard disk. Once the review is complete, the image copies can be deleted from the hard disk, and they still remain on the tape.

Standard Backup Procedures:

1. Raw Data - daily backup (MOVE) to tape, once scan slice reconstruction is complete, whether or not SA or ECA is analyzed

2. IMAGE Data - backup (MOVE) to Tape, only after the scans are fully analyzed, all data is cleaned, including outliers having been reviewed by PI's

3. Database Backup (DB Backup) - performed weekly.

   Example: Week one - Use Tape Cartridge labeled QC 1

Week two - Use Tape Cartridge labeled QC 2

This will minimize the amount of data lost if one DB Backup tape is lost.

4. Operating System (OS) backup - Scanco recommends that the operating system be backed up every 6 months. The system displays an alert when opening a Session when the OS backup is due. In the event of a loss to operating system, this would reduce the amount of time needed to reconstruct the files. The separate tape cartridge used to back up the operating system is labeled "OS Backup".

Secure Storage:

There are two fire-safe, waterproof boxes for the storage of all backup/archive tapes. One safe box is used to store all daily RAW data backup, weekly RAW data backup (called weekly DB), and Operating System backup archived every 6 months. This safe box is kept in the horizontal locked cabinet in clinic room 106. The second safe box is used to store all IMAGES backed up to tape and this box is locked and kept in clinic room 104. The boxes are kept in different rooms to reduce the risk of losing all tapes in an unexpected facility event.

Note: The actual HR-pQCT results files are uploaded to the research shared drive at Hebrew SeniorLife using Sharefile Secure File Transfer. This procedure is described below.

B. Transfer HR-pQCT Standard Analysis Results Data to HSL (Monthly)

The technologist will create two database files (5=direct trabecular variable results; 6=direct cortical variable results) at the HR-pQCT terminal as follows:

1. [redacted]

[redacted]

Transfer via Sharefile

Upload to HSL Research Shared Drive via Sharefile:

[redacted]

C. Transfer to University of Calgary (Micro Finite Element Analysis (mFEA)

After Trabecular and Cortical analysis, and all QA procedures are completed the scans may be sent to Dr. Steven Boyd at the University of Calgary for generation of mFEA measures.

Check that the scan file range is present on the HR-pQCT workstation in the mFEA duplicates folder

a) field tech uploads inventory files – mfea duplicates inventory MMDDYYYY.txt
   (1) a listing of all mfea files on the scanner
   (2) produced by mfea.inventory.cmd
b) info.txt

   (1) a listing of all scans and their status that have been acquired on the scanner
   (2) produced by Scanco script

c) programmer cross references duplicates inventory and all scan listing
   (1) any discrepancies are reported and referred to field tech for investigation
   (2) iterate steps a. and b. as necessary

1. Using clinic workstation, copy duplicate files to Sharefile via Drive Mapper
2. Verify that scan files are present in Sharefile
3. [redacted]

   b. [redacted]

D. Transfer mFEA files via Sharefile

1. [redacted]

[redacted] Wait [redacted] r the [redacted] step 1

12. Quality Assurance of Imaging

A. Motion Artifact Grading

1. The motion artifact grade is assigned by the bone technologist based on a visual review of scan image slices. The Scanco Guidelines for Motion Artifact Grades are used. The grade is recorded in the HR-pQCT logbook, but is not recorded in the HR-pQCT. Each scan must be assigned a motion artifact grade in REDCap to identify it as an evaluable scan for bone microarchitecture or volumetric BMD, or as an unevaluable scan for any measure. The technologist enters the motion artifact grade from her logbook entry into REDCap. It is imperative that the grades in REDCap are accurate. Once a week, a dual control system of data entry verification is performed to ensure accuracy. The following 5-point scale is used and entered into REDCap:

Grade 1 = No movement (highly acceptable)

Grade 2 = Slight movement (very acceptable)

Grade 3 = Some movement (acceptable)

Grade 4 = Moderate movement (acceptable for some measures but not all)

Grade 5 = Severe movement (unacceptable)

The bone technologist and the project director will work together to verify the accuracy of REDCap data entry of grades once a week. They also verify the accuracy of scan measurement numbers to keep in the database when a scan is repeated and has two measurement numbers for the same body site.

2. In tandem, the bone technologist references the HR-pQCT logbook, and the project director logs into REDCap to verify data entry.

a) Click on username

b) Select username at dropdown menu

c) Enter password (if it does not appear automatically)

d) Log in

3. Under 'My Projects' on top left toolbar

a) Click "Framingham Osteoporosis Study Offspring Exam 10/Omni1 Exam 5 Questionnaire"

b) Click on 'Add/Edit Records' at the far left under 'REDCap' and under 'Data Collection'

4. Next to: "Choose an existing Framingham Heart Study ID"

a) Press arrow (Select Records) and scroll down

b) Find participant ID provided by bone technologist

c) Click on it once

5. "Event Grid" appears. Click to open CTScan QC form, where motion artifact grades are entered.

(A green dot = motion artifact form is completed)

(A red dot = motion artifact form is not completed)

6. The technologist reviews the HR-pQCT exam logbook for participant's forearm/radius scan and associated motion artifact grade. Grade 1 – 5 is circled in the comments section. The technologist may also review the forearm scan online to confirm the quality grade. The technologist states out loud the site (e.g. left radius/right radius) and the motion artifact grades which the bone technologist confirms are entered in REDCap CT Scan QC form. If the grade in REDCap does not match the logbook entry, the technologist reviews the scan analysis to confirm the grade, and the correct grade is recorded in the logbook and in REDCap.

7. The technologist records an "X" in the "R" (REDCap) column of the logbook to confirm that the data entry verification was done.

8. If a scan was repeated, the form displays: "Forearm (or Tibia) measurement number (M-No) to keep in database." If there was no repeat scan, this statement will not appear.

a) The bone technologist states out loud the Measurement number (scan) to keep. NOTE: Only one scan will be kept and only if the scan is evaluable with a grade of 1, 2, 3 or 4. If both scans are graded "5', neither scan is acceptable and the field is left blank.

b) The project director confirms that the correct measurement number is entered in REDCap, corrects it if necessary, and clicks 'Save'.

c) If there was a repeat measurement, the project director opens the Scan Info form, even if a green dot for completed is displayed. The entries are confirmed for 1) measurement numbers for first and repeat scans; 2) Are MeasNos acceptable 'Yes' or 'No'

d) The project director clicks Save and Complete.

9. Steps 6, 7, and 8 are repeated (if there was a repeat leg/tibia scan), to verify the motion artifact grade for the leg/tibia scan.

10. Under "Form Status: Complete?

Scroll down and select "Complete"

11. Click "Save and Continue"

NOTE: Dot should be green, indicating completion. If dot does not turn green, the section is not complete or is missing data. An error message will appear if any information is missing, preventing you from moving on to the next screen.

This is true of all sections:

- Participant_Info
- Scan_Info (if any information is missing, check HR-pQCT system records, DXA system records, and corresponding exam logbooks.
- Misc
- CTScan_QC

To continue to verify other motion artifact grades:

Click “Select other record” on the left corner of REDCap screen under “Framingham Heart Study ID”.

B. Image Quality

1) HR-pQCT images which the ISCD-certified technologist escalates for a second opinion are reviewed and adjudicated by the Co-investigator, Dr. Bouxsein and PI as needed. Additionally, distributions of all variables of interest are run to identify extreme observations. Scans with extreme observations of either standard analysis (SA) and/or endo-cortical analysis (ECA) variables are examined and adjudicated by Dr. Bouxsein or PI.
2) The clinic technologist records any atypical information about a participant’s exam (e.g., physical challenges, or medical conditions) on the HR-pQCT exam logbook. These records may be referenced during review of images to help corroborate technical quality.

13. Common Operational Practices & Solutions

X-ray Tube Replacement for the FOS leased XtremeCT machine (Scanco's ID # HSL 3342 for our device)

The type of x-ray tube used in the HR-pQCT is designed to last from 6 months to one year. Since HSL is leasing the equipment, all service and replacement parts are covered by the manufacturer, Scanco Medical based in Switzerland. When a new x-ray tube is required, it is shipped from Europe via FEDEX overnight to the Framingham clinic, and a Scanco technician travels to the U.S. to install it. The HR-pQCT is unavailable for one day for the installation. The installation takes about 3 – 4 hours, and recalibration and testing takes from 1 – 2 hours.

- The technologist should see warning or error messages in the days or weeks prior to an x-ray tube failure. Example: “X-ray tube mon.control – intensity too low”

  If this or similar messages appear, the technologist shall immediately email [redacted] to inform them.

- The x-ray tube should run at a normal intensity level of 900uA. The message above may indicate that the intensity level is below 900uA which is not optimal for

scanning. NOTE: *Scanco will need remote access to take the system offline and increase the intensity to 900uA. This procedure may allow scanning to continue for a short time, but the intensity level will not hold at the optimal level, and the machine may be unreliable.

- If Scanco reports that we have performed scans at a low intensity (below 900uA), the technologist records on the HR-pQCT exam logs which scans are affected for future reference in case there are questions about the scan results.
- To escalate a support issue, the technologist or project director may contact : Rasesh Kapadia rkapadia@scanco.ch

Phone: In PA, U.S. – Available at clinic in office number posted on wall

- Prior to sending a new x-ray tube, Scanco runs performance tests on the new x-ray tube and ships it via FEDEX overnight to the clinic using the following address:

FRAMINGHAM HEART STUDY

[redacted]

- Scano emails the technologist and project director the FEDEX tracking number so we can track shipment progress. The package containing the new x-ray tube will go through U.S. Customs before being released for delivery to the Framingham clinic.

- A FEDEX agent will contact [redacted] as the recipient, asking that a U.S. Customs Import document (Importer ID form) be completed and returned expeditiously. FEDEX will fax the form to be completed to the fax number we provide.
- The technologist or project director completes the Importer ID form, verifying our Importer Name, shipping address information and HSL's Tax ID number. *See sample of the U.S. Importer ID form below.* The key information to provide on the Importer ID Form is:

[redacted]

Importer Mailing Address:

FRAMINGHAM HEART STUDY

[redacted]

- Technologist or project director faxes the form back to the FEDEX agent who then works to have the package cleared through U.S. Customs.

- In parallel, Scanco schedules a technician to travel to the clinic to install the x-ray tube. The technologist notifies Scanco, or the technician assigned, when the package arrives and schedules the installation.

- Also in parallel, the technologist notifies the FHS Scheduling Coordinator of the expected downtime.

- Scanco Support will *remotely access the Framingham HR-pQCT when installation and recalibration is complete in order to provide an updated quality control reference range.

- The project director will update all clinic procedural documents to reflect any change to the daily quality control reference range for the HR-pQCT.

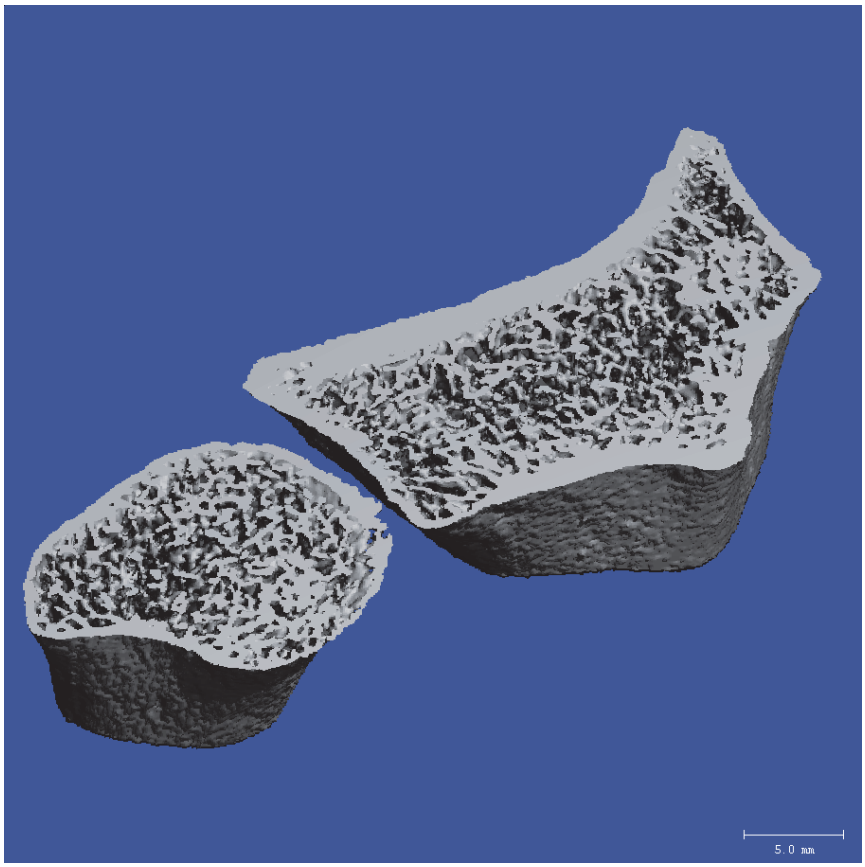
  *Scanco's remote access to HR-pQCT: The Framingham IT Manager must be contacted by Scanco to activate their VPN account ([redacted] The IT Manager will grant Scanco access through the Framingham Network to diagnose and complete any temporary adjustments, and to perform any follow up measures. This access is typically granted for a few days.

XtremeCT II

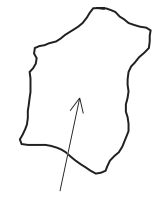
SCANCO MEDICAL

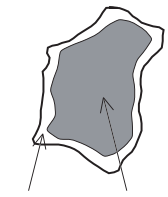
Hans Muster

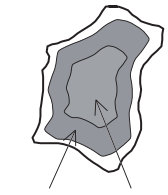
Site:	Radius		
Pat-No.:	10	Filename:	C0000300
M-No.:	310	Date:	12-MAR-2017 10:31
Born:	01.01.1949	Age:	68



Mean Area of Slices [mm^2]: 425







Densities			Structure		
D100	[mg HA/ccm]	283	BV/TV	[1]	0.177
Dtrab	[mg HA/ccm]	212	Tb.N	[1/mm]	2.420
Dmeta	[mg HA/ccm]	345	Tb.Th	[mm]	0.073
Dinn	[mg HA/ccm]	122	Tb.Sp	[mm]	0.340
Ratio: Meta/Inn	[1]	2.83	Tb.1/N.SD	[mm]	0.068
Dcort	[mg HA/ccm]	729	C.Th	[mm]	0.27

D100	Average Bone Density	BV/TV	Trab. Bone Volume to Tissue Volume
Dtrab	Trabecular Bone Density	Tb.N	Number of Trabeculae
Dmeta	Meta Trab. Bone Density	Tb.Th	Trabecular Thickness
Dinn	Inner Trab. Bone Density	Tb.Sp	Trabecular Separation
Meta/Inn	Ratio Meta to Inner Density	Tb.1/N.SD	StDev of 1/Tb.N: Inhomogeneity of Network
Dcort	Cortical Bone Density	C.Th	Cortical Thickness

XtremeCT II

Specifications:

Field of View:	140 mm
Max. Scan Length:	225 mm
Resolution (10% MTF):	> 8.5 lp/mm (<58 µm)
Voxel Size:	17 - 273 µm
Image Matrix:	512 x 512 up to 8192 x 8192

Patient protocol I:

Image matrix:	2304 x 2304
Measurement time per stack (168 slices):	2.1 min
For a patient scan with voxel size:	60 µm

Patient protocol II (XtremeCT compatible):

Image matrix:	1708 x 1708
Measurement time per stack (123 slices):	1.4 min
For a patient scan with voxel size:	82 µm

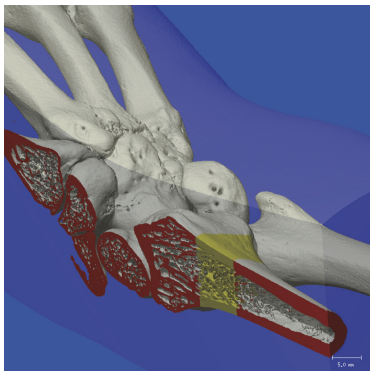
Detector Size:	4608 x 400 [pixels], 221 mm x 19.5 mm
X-ray :	68 kVp, 100 W Focal Spot Size: 60 µm Target: W
Effective Dose:	<5 µSv per measurement (ICRP91)
Weight:	570 kg
Size (WxDxH):	1.42 m x 0.96 m x 1.42 m (scanner only)
Included Accessories:	Chair, hand and foot casts, powerful computer workstation and software
Beam Geometry:	Cone Beam

The New Dimension in Bone Quality Assessement

The XtremeCT II is the new generation high resolution peripheral quantitative computed tomography (HR-pQCT).

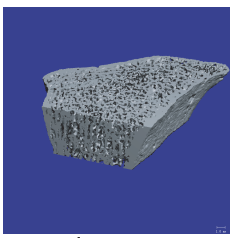
The XtremeCT II is designed to measure the bone density and to quantify the threedimensional microarchitecture of the bone at the distal radius and tibia at an even higher precision and speed than its predecessor, the XtremeCT. The system is designed to be used for research and treatment monitoring of osteoporosis.

Density Parameters:
- Cortical and Trabecular Density in Different Regions
- BMD and BMC



Structural Parameters:
- Trabecular Thickness
- Trabecular Separation
- Trabecular Number
- Volume Fraction
- Cortical Thickness
- Cortical porosity
- Arterial calcification

Registration of 3D-Region of Interest for Follow-up Scans (Common Region)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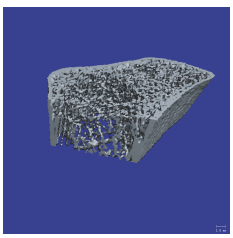
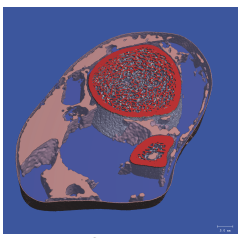
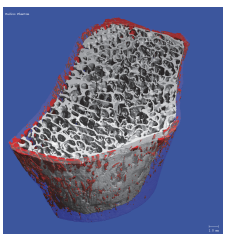
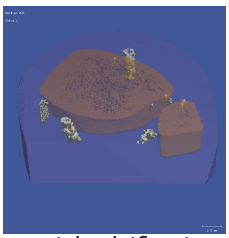

osteoporotic


muscle fat separation


cortical porosity


arterial calcification

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V4/12-2018

CE, CSA approved
Please contact Scanco Medical for latest update on regulatory approval status in your country.

High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT) Bone Study

Questionnaire

Offspring Cohort Examination 10/ Omni1 Cohort Examination 5

This document includes the following questionnaires and data capture forms for the Bone Study

- Pre-Scan Eligibility Questionnaire
- Determine Scan Side Questionnaire
- Scan Information
- Scan Quality Grade

Offspring Cohort Examination 10/Omni1 Cohort Examination 5

Framingham Bone Study Pre-Scan Eligibility Questionnaire

Framingham Heart Study ID fhsid
[___][___].[___][___][___][___]

What Cohort is the Participant? idtype
|___| [2] Off [X] Omni1

Clinic Exam Date clinic-exam_date
[___][___].[___][___] [___][___][___][___] M-D-Y

Have you had a nuclear medicine scan in the last seven (7) days? med_scan_g302
[___] [0] No [1] Yes

- **If Yes, Reschedule for minimum 8 days after nuclear medicine scan** med_scan_resch_g302
  [___][___].[___][___] [___][___][___][___] M-D-Y

Gender gdr_g3o2
[___] [1] Male [1] Female

- BLANK

- **Eligible for scanning** elig_g3o2
  [___] [0] No [1] Yes

Reason why not eligible for scanning? elig_na_g3o2
[___] [1] X
[2] X
[3] Nuclear medicine scan
[7] Other

Specify Other elig_na_oth_g3o2

_____

Examiner Name examiner

[___] [1] Danette Carroll
[X]
[X]

HR-pQCT Sample Number (s-No.) Scfqct_snum
[___][___].[___][___][___][___] Enter O if no HR-pQCT scan done

Determine HR-pQCT Forearm Scan Side

1. For majority of activities (not just writing), which hand is used? scfqct_domn
|___| [1] Right [2] Left [3] Equal

2. Have you ever fractured your non-dominant forearm?

|___| [0] No [1] Yes

- If YES: **2a Have you ever fractured your dominant forearm**?
  [___] [0] No [1] Yes
- If YES: **2b Scan the forearm with the oldest fracture**
  [___] [1] Right [2] Left
- If NO: **2c Scan dominant forearm**
  [___] [1] Right [2] Left

2d If NO, never fractured non-dominant forearm, scan the non dominant side

[___] [1] Right [2] Left (If equal, scan left forearm)

Determine HR-pQCT Leg Scan Side

3 Have you ever had an ankle fracture or a knee replacement? sclqct_kraf_g3o2
[___] [0] No [1] Yes If No, scan right leg

If [sclqct_kraf_g3o2] = '1'
3a Check any that apply sclqct_kraf
[___] [1] Right ankle fractured
[___] [2] Right knee replaced
[___] [3 Left ankle fractured
[___] [4] Left knee replaced

If [sclqct_kraf_g3o2] = '1' and [sclqct_kraf(1)] = '1' and [sclqct_kraf(3)] = '1'
3b If both ankles were fractured, scan the leg with the oldest fracture sclqct_chooseside
[___] [1] Right [2] Left

If [sclqct_kraf_g3o2] = '1' and [sclqct_kraf(2)] = '1' and [sclqct_kraf(4)] = '1'
3c If both knees were replaced, scan the leg side based on participant's comfort sclqct_kf_g3o2
[___] [1] Right [2] Left

If [sclqct_kraf_g3o2] = '0'
3z Leg should be scanned on this side: sclqct_prfside
|___| [1] Right [2] Left

HR-pQCT Leg Scan Information

3z Leg should be scanned on this side: sclqct_prfside

|___| [1] Right [2] Left

5 Leg HR-pQCT scanned? sclct

[___] [0] No [1] Yes

scfqct_llength_g3o2

5a Leg length

[___][___].[___][___] mm

- **IF NO** [sclct] = '0'

  5b Select a reason why neither leg is scanned: sclqct_whynotsc_g3o2

  [___] [1] X
  [___] [2] X
  [___] [3] Metal presence
  [___] [4] Exceed size/weight limit
  [___] [5] Tremor
  [___] [6] Refused
  [___] [7] Other
  [___] [8] Coughing
  [___] [9] Parkinson's
  [___] [10] Peripheral neuropathy
  [___] [11] Pain

  [sclqct_whynotsc_g3o2] = '4' and [sclct] = '0'

  5c Specify size or weight sclqct_whynot_sw_g3o2

  [___] [4a] Size
  [___] [4b] Weight

  [sclqct_whynotsc_g3o2] = '4' and [sclct] = '0'

  5d Comment on size and/or weight sclqct_whynot_swc_g3o2

_____

  [sclqct_whynotsc_g3o2] = '6' and [sclct] = '0'

  5e Specify refused sclgct_whynotsc_ref_g3o2

_____

  [sclct] = '1' and [sclqct_prf_g3o2] = '0' and
  [sclqct_whynotpref_g3o2] = '7'

  5f Specify other sclqct_whynotpref_oth_g3o2

_____

- **IF YES** [sclct] = ‘1’

5g Is preferred leg scanned? sclqct_prf_g3o2
[___] [0] No [1] Yes

[sclct] = '1' and [sclqct_prf_g3o2] = '0'
5h Reason why preferred leg side was not scanned? sclqct_whynotpref_g3o2
[___] [3] Metal presence
[___] [5] Tremor
[___] [7] Other
[___] [11] Pain
[___] [12] Cast

[sclct] = '1' y [sclqct_prf_g3o2] = '0' y [sclqct_whynotpref_g3o2] = '7'
5i Specify other sclqct_whynotpref_oth_g3o2
_____

[sclct] = '1'
5j 1st leg measurement number (M-No.) sclqct_mnum1
|___|___|___|___|

[sclct] = '1'
5k Is 1st leg scan acceptable? sclqct_ok
[___] [0] No [1] Yes

[sclct] = '1' and [sclqct_ok] = '0'
5l Leg scan repeated? sclqct_rpt
[___] [0] No [1] Yes

[sclct] = '1' and [sclqct_rpt] = '1'
5m 2nd leg measurement number (M-No.) sclqct_mnum2
|___|___|___|___|

HR-pQCT Forearm Scan Information

2z Forearm should be scanned on this side: scfqct_prfside
|___| [1] Right [2] Left

6 Is HR-pQCT forearm scanned? scfqct_g3o2
[___] [0] No [1] Yes

6a Forearm length scfqct_flenght_g3o2
[___][___].[___][___] mm

[scfqct_g3o2] = '0'

- **6b If no, and neither forearm is scanned, select the reason** noscfqct
  [___] [1] BLANK
  [___] [2] BLANK
  [___] [3] Metal presence
  [___] [4] Exceed size/weight limit
  [___] [5] Tremor
  [___] [6] Refused
  [___] [7] Other
  [___] [8] Coughing
  [___] [9] Parkinson's
  [___] [10] Peripheral neuropathy
  [___] [11] Pain

  [noscfqct] = '4' and [scfqct_pscyn] = '0'
  6bc Specify size or weight noscfqct_sw_g3o2
  [___] 4a Size 4b Weight

  [noscfqct] = '4' and [scfqct_pscyn] = '0'
  6d Comment on size and/or weight noscfqct_swc_g3o2
  _____

  [scfqct_g3o2] = '0' and [noscfqct] = '6'
  6e Specify the reason why forearm HR-pQCT scan was refused noscfqct_ref
  _____

  [scfqct_g3o2] = '0' and [noscfqct] = '7'
  6f Specify "other" reason why forearm HR-pQCT scan not taken noscfqct_oth

- **If YES** [scfqct_g3o2] = '1'
  6g Is preferred forearm scanned scfqct_pscyn
  [___] [0] No [1] Yes

[scfqct_pscyn] = '0'

6h Select a reason why preferred forearm side was not scanned scfqct_whynotpref

[___] [3] Metal presence
[___] [7] Other
[___] [11] Pain (in shoulder)
[___] [12] Cast/bracelet

[scfqct_pscyn] = '0' and [scfqct_whynotpref] = '7'

6i Specify other scfqct_whynotpref_oth_g3o2

_____

[scfqct_g3o2] = '1'

6j 1st forearm measurement number (M-No.) scfqct_mnum1

|___|___|___|___|

[scfqct_g3o2] = '1'

6k Is 1st forearm scan acceptable? scfqct_ok

[___] [0] No [1] Yes

[scfqct_g3o2] = '1' and [scfqct_ok] = '0'

6l Forearm scan repeated? scfqct_rpt

[___] [0] No [1] Yes

[scfqct_rpt] = '1' and [scfqct_ok] = '0'

6m 2nd forearm measurement number (M-No.) scfqct_mnum2

|___|___|___|___|

HR-pQCT Scan Quality Grade

[scfqct_ok] = '0' and [scfqct_rpt] = '1'

12 Is either forearm scan acceptable? scfqct_bothbad

|___| [0] No [1] Yes

[scfqct_ok] = '0' and [scfqct_rpt] = '1'

12a Forearm measurement number (M-No.) to keep in the database scfqct_anum

|___|___|___|___|

12b Artifact Grade Forearm artifact_grade

|___| Grade 1
|___| Grade 2
|___| Grade 3
|___| Grade 4
|___| Grade 5

[sclqct_ok] = '0' and [sclqct_rpt] = '1'

13 Is either leg scan acceptable? sclqct_bothbad

|___| [0] No [1] Yes

[sclqct_ok] = '0' and [sclqct_rpt] = '1'

13a Leg measurement number (M-No.) to keep in the database sclqct_anum

|___|___|___|___|

13b Artifact Grade Leg artifact_grade2

|___| Grade 1
|___| Grade 2
|___| Grade 3
|___| Grade 4
|___| Grade 5

"Vascular Mechanisms Underlying Skeletal Fragility"
R01 AG065299
Draft Language
Consent, Bone Study
(PI: Samelson)

Bone Scan: We are interested in learning about how the skeleton changes with aging. We will ask you to participate in two bone scans to examine the bone structure in your lower leg and lower arm. The scan is a non-invasive and painless test, and provides a detailed image of the "micro-architecture" inside the bone. Each scan takes about two minutes and requires that you keep as still as possible.

What risks can I expect? Bone scans involve the use of x-rays, a form of energy also called radiation. Exposure to radiation is measured in units called microsieverts (µSv). The amount of radiation for each leg or arm bone scan is less than 5 µSv per scan. This is a low radiation dose compared to other common imaging procedures. For example, a chest x-ray has an effective dose of 100 µSv. Further, the radiation exposure from each bone scan is less than the amount of background radiation in the U.S., estimated at approximately 8 µSv per day. Since we will perform one scan of the leg and another scan of the arm, the total effective radiation dose for the two scans together will be less than 10 µSv, only slightly more than the amount of everyday background radiation. Occasionally, a scan may need to be repeated if the arm or leg was not held still during the imaging. This would increase the amount of radiation from 10 µSv to 15 to 20 µSv. This amount is still less than one-fifth the exposure from a chest x-ray and equal to about two and a half days of everyday background radiation (8 µSv per day). Since the amount of radiation from the bone scans is so small, there are no known long term effects of this radiation on your health.

There are some situations that can exclude individuals from participating in the bone scan. Individuals who are not able to hold their arm or leg still for two to three minutes will not be eligible, since the image quality will not be adequate. Persons weighing more than 330 pounds will not be able to participate due to the weight limit of the chair of the scanner. Persons who have had a nuclear medicine scan in the past seven days will not be eligible as radioactive tracers could affect the bone measurements. However, these participants are invited to come back for bone scanning at a later date, after a minimum of eight days since the nuclear medicine scan.

Technician, Bone Study
(PI: Samelson)

To minimize the number of technicians, as per Covid-19 guidelines, the Bone Study (PI: Samelson) and Muscle Study ([redacted] is a trained bone technologist, certified by the International Society for Clinical Densitometry. [redacted] is highly experienced having worked with the Bone Study at the Framingham Heart Study research center for many years.

[redacted]

* Additional field staff will be hired as needed

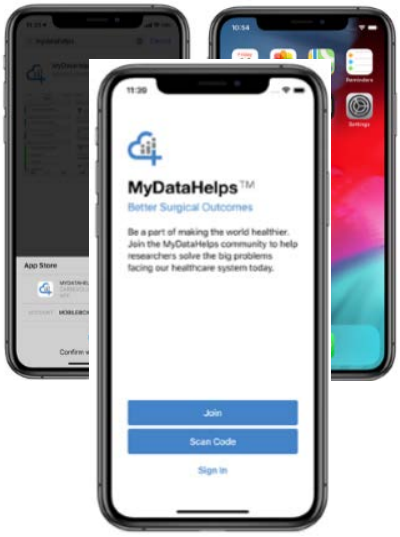
eFHS Manual of Procedures

Table of Contents

I. Downloading The MyDataHelps to the iPhone

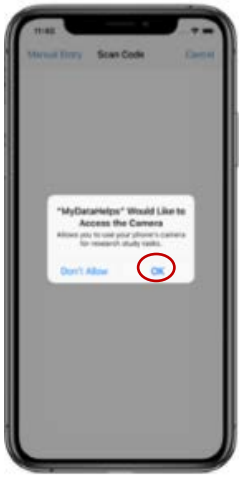
The MyDataHelps app is downloaded exactly as you would any other free iPhone app. Please remember that to download any apps, you must have access to the password for your Apple ID. First, you should open the app store on your phone and search for “MyDataHelps”:

The MyDataHelps app should be the first result. You can then tap the “GET” button, which will turn into “OPEN.” Tapping “OPEN” may prompt you to enter your Apple ID (or the touch or side button install). After entering your password (or using face recognition), the MyDataHelps app will begin downloading and then appear on your home screen.



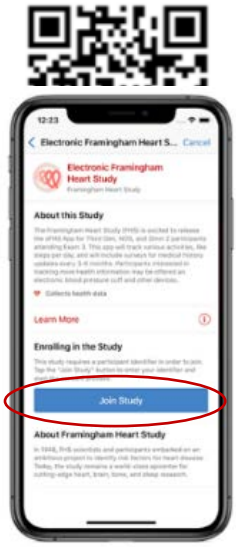
Open the MyDataHelps app on your phone. You should see this welcome screen:

Please select "Scan Code" and you will be prompted to allow camera access and should select



"OK"

Once the camera has been opened, Scan the QR code or manually enter it: [redacted]"



Now, you will be asked to join the eFHS Offspring/Omni 1 study. Click “Join Study” to proceed.

To continue joining the eFHS study, you will need to enter the participant’s eFHS ID. (You can look up a participant’s eFHS ID in the RANID spreadsheet).

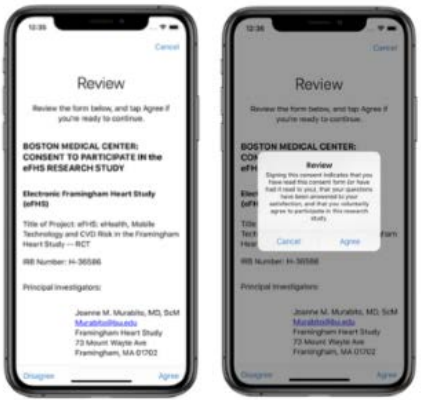
You will then be prompted to enter basic demographic information, including an email address. The MyDataHelps app will save this information. The participant will need to make a password; this password must be at least 8 characters long and include at least 1 capital and lowercase letter, and a special character (i.e. a number or symbol). They may also be prompted to save their password to their keychain; this is optional.

Once the participant has entered their demographic information, they will be asked to review and agree to the MyDataHelps Privacy Policy to understand how their data will be used. Here you can prompt them to read as much or as little as they would like, and tap agree when they are ready. Now they will be asked to sign the agreement using their finger.

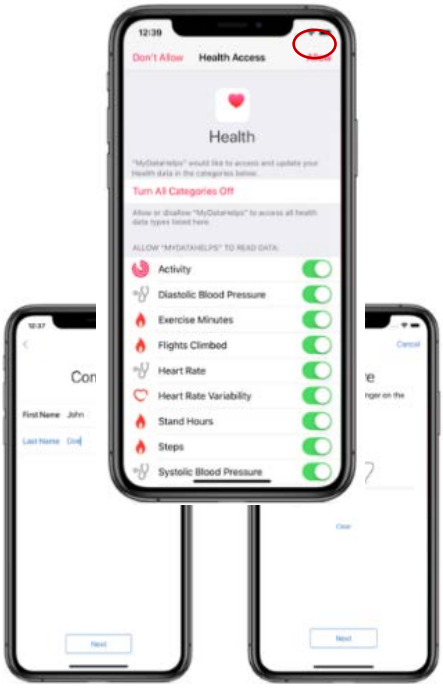
Next, you will be prompted to enable notifications. When prompted, select “OK.” When asked

whether to allow notifications, please select “Allow”. We will only send the participant notifications once per week to let them know if we have received their data, and once every two to four weeks when their surveys are ready.

Now that the participant is registered with MyDataHelps, the app will present the eFHS consent document for them to review and accept. They must select “Agree” to participate in eFHS study.



To complete consent, participants will be asked to enter their name and sign with their finger. Consent must be completed to participate in eFHS.
Finally, you will see permissions prompts to approve the sharing of Apple Health Data. You should turn all categories on using the “Turn All Categories On” button. Once all categories are on, you should tap the “Allow” button in the top right, so the app can read data from Apple Health.



What happens if a participant does not have an email address?

If a participant does not have an email address, they will need to create one to participate in the eFHS study. [redacted]

What are the requirements for running the MyDataHelps app on the participant’s phone?

For Apple devices, MyDataHelps is supported on iPhone, iPad, Apple Watch, and iPod touch running iOS 10.0 or higher. For Android devices, MyDataHelps requires Android version 7.0 or higher.

II. Pairing The Apple Watch

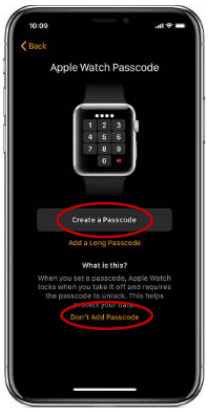
1. Hold your Apple Watch close to the iPhone
    - Wait for the "Use your iPhone to set up this Apple Watch" message to appear on the iPhone, then tap Continue. If you don't see this message, open the Apple Watch app, then tap Start Pairing.
    - Keep the Apple Watch and iPhone close together until you complete these

steps.

2. Hold your iPhone over the animation
    - Center the watch face in the viewfinder on the iPhone. Wait for a message to say that your Apple Watch is paired.
    - If you can't use the camera, tap Pair Apple Watch Manually, then follow the steps that appear.

3. Have the participant sign in with their Apple ID
    - If the participant remembers their Apple ID password, have them enter it. If they don’t remember their password, they can sign in later from the Apple Watch app: (Tap General > Apple ID, then sign in).

4. Choose settings
    - The Apple Watch shows you which settings it shares with your iPhone. If you turned on Find my iPhone, Location Services, Wi-Fi Calling, and Diagnostics for your iPhone, these settings automatically turn on for your Apple Watch.
    - You can choose to use other settings, like Route Tracking and Siri. If Siri isn't already set up on your iPhone, it will turn on after you choose this option.
    - The participant can set up their watch any way that they like, nothing that they do or change here should interfere with us receiving data from their device.
5. Create a passcode
    - The participant can choose to skip creating a passcode, but they need one for features like Apple Pay (which of course, does not matter to us).
    - On their iPhone, tap Create a Passcode or Add a Long Passcode, then switch to the Apple Watch to enter their new code. To skip, tap "Don't Add Passcode".



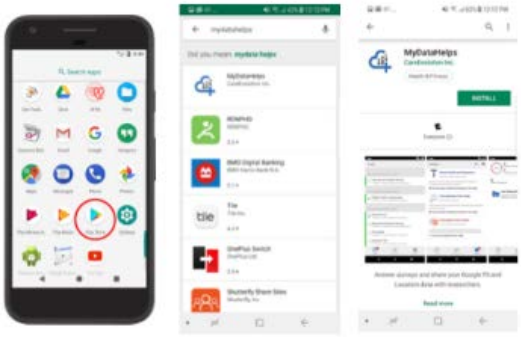
6. Choose features and apps
    - The Apple Watch set-up on the phone will walk you through setting up features like SOS and Activity. Then, the participant can choose if they would like to add the apps from their phone to their watch. This includes any app that the participant installed on the phone themselves (the watch comes with a set of preloaded apps already on it – similarly to when you get a new iPhone). We let

the participant decide what is best for them, but might recommend tapping "Choose Later" because they don't need to have any apps on the watch, and they can get confusing.

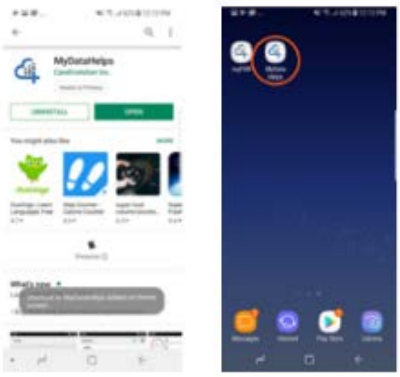
7. Wait for Devices to Sync
    - Depending on how much data they have, syncing might take some time. The participant does not need to wait in the office while they wait for their watch to sync. They can leave, just make sure to tell them to keep their devices close together (30 ft.) until you hear a chime and feel a gentle tap from your Apple Watch, then the devices will be paired, and sharing data with eFHS.

III. Downloading the MyDataHelps App for Android

The MyDataHelps app is downloaded exactly as you would any other free Android app. Please remember that to download any apps, you must have access to the password for your Google Account. First, open the Play Store, and search for "MyDataHelps":



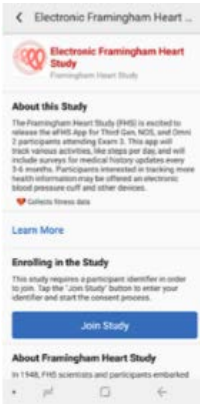
The MyDataHelps app should be the first result. You can then tap the "INSTALL" button. The app should begin downloading. When the download is complete the "INSTALL" button will change to "Done" and an icon should be added to the home screen.



Open the MyDataHelps app on your phone. You should see this welcome screen:

You should tap the “Scan Code” button to begin the registration process, then you may be prompted to allow camera access and should select “yes". Once your camera has opened you will scan this QR Code or manually enter code: [redacted]

On the next screen, you will be asked to join the eFHS Offspring/ Omni 1 study. Click “Join

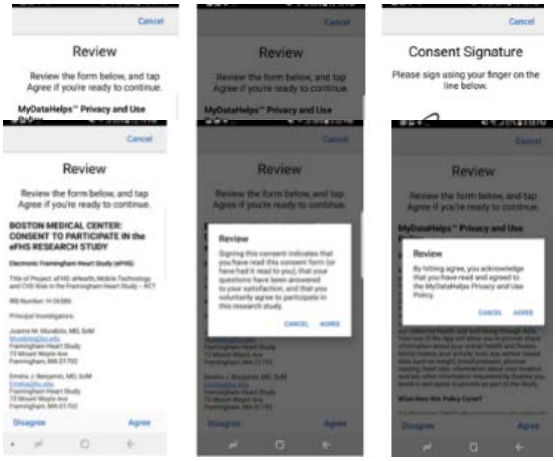


Study” to proceed.

To continue joining the eFHS study, you will need to enter the participant’s eFHS ID (you can find this in the RANID Spreadsheet). After completing this form, you should tap the “Next” button to continue registration.

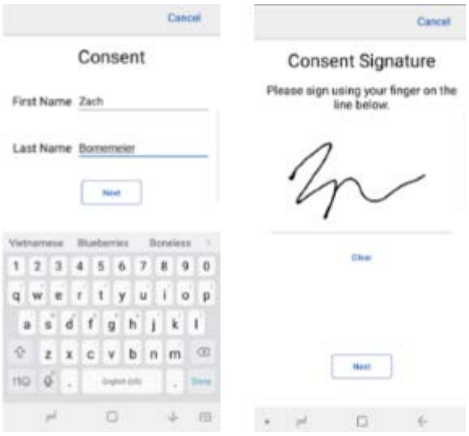
The participant will then be prompted to enter basic demographic information, including their email address.

Now that the participant has entered their demographic information, they will be asked to review and agree to the MyDataHelps Privacy Policy to understand how their data will be used.

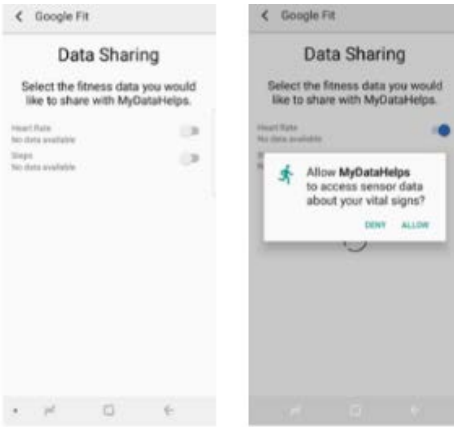


Now that the participant is registered with MyDataHelps, the app will present the eFHS consent document to review and accept. They must select “Agree” to participate in the eFHS study.

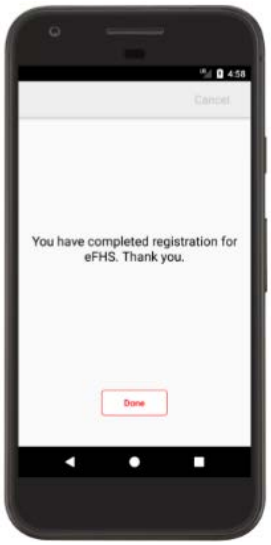
To complete consent, they will be asked to enter their name and sign with their finger. Consent must be completed to participate in eFHS.



Finally, the participant will receive a prompt to approve the sharing of Google Fit data. Please grant access for heart rate, weight, and steps (all available catagories).



Registration is now completed!



IV. T20 Form in REDCap

- When a participant comes to the eFHS station in the Research Center, or you are enrolling the participant in eFHS over the phone or zoom, you must use the T20 form in REDCap to document
- To access the form please ask Hongshan, Liu (FHS data management) to give permissions to your account to access the form and be added to the tech ID list for this form
- To access the form go to REDCap, login with your username and password, select Offspring Exam 10, Omni 1 Exam 5, and then select "T20-eFHS device" tracking on the left hand side under "Data Collection"
- Follow the form step by step inputting the start and end time, your technician ID, and the questions that follow. Please input any notes in the eFHS Worksheet that is displayed at the bottom of the form under "Additional Comments"
- If a participant switches their phone during their enrollment in eFHS please refer back to this form to document the day they switched their phone and the phone types they switched from and to.

V. Short and Long Protocols for Participants

- When a participant is interested in eFHS please either give them the short or long protocol depending on their enrollment status, and phone type
- If the ppt has enrolled with the coordinator they will receive a short protocol
- If the ppt will enroll at home, they will receive a long protocol which includes step by step directions on how to download and enroll in eFHS
- Short and long protocols exist for iPhone, Android, and Computer
- Protocols are located in the K drive under K>eFHS>Heather>Offspring App>Protocols

VI. RCT Protocol

- On **6/09/21** a new protocol for the randomized control trial was approved by the IRB
- Participants began receiving this protocol on **6/21/21**
- The trial randomizes participants into two groups (2 week surveys and 4 week surveys) The participants in 2 week survey group will receive the surveys every two weeks and participants in the 4 week group will receive all the surveys at once every 4 weeks.
- The script for the RCT is as follows: *We are distributing the same number of surveys at either 2- or 4-week intervals, and we are asking for your consent to be randomly assigned to one of these schedules so we can study the effect on the overall response rate".*

- The step by step process on how to enroll participants in the RCT is located in the K drive under K>eFHS>Heather>Offspring App>Protocols> RK Studios Enrollment Protocol for RCT

VII. Stroop Protocol

- When administering surveys and enrolling the ppt in the MyDataHelps app please follow the following stroop protocol to determine whether or not the participant can participate in the stroop survey:
- Ask the participant "*One of our surveys requires you to be able to distinguish colors. Do you have any difficulty seeing the colors red, green, blue, or yellow?*"
- If the participant answers "Yes" they do have difficulty seeing any or a few of these colors you must log their eFHS ID in the K-1wk follow up and mars question script document in the K drive under K>eFHS>Heather>Offspring App. The tab on the excel file named "stroop" is where you will enter the ppt eFHS ID, their initials, and the date you manually deleted the survey
- You must continue to monitor this participant and delete their stroop survey whenever new surveys are made available
- This is also considered a corrective action and must be documented in the corrective action tab in the same file.

VIII. Corrective Actions

- All corrective Actions must be documented for eFHS Offspring/ Omni 1
- The document in the K drive under K>eFHS>Heather>Offspring App> K-1wk follow up and mars question script contains a tab labeled "Corrective Actions" where they must be logged
- Please log the date, eFHS ID, the problem, and the correction

IX. RK Studios Manual

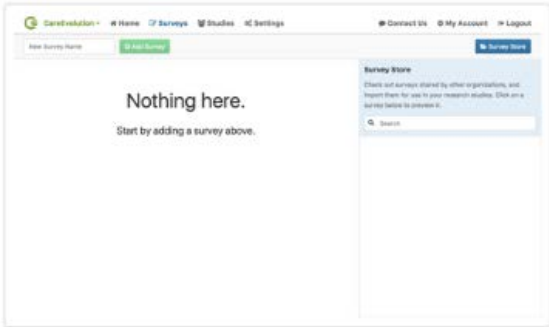
- For all questions pertaining to RK Studios please refer to the RK Studios Manual before contacting our Care Evolution/RK Studios partner
- https://rkstudio-support.careevolution.com/hc/en-us
- The link above contains information on how to create surveys, add/ invite participants, notifications, project management, data export, and much more.

X. Creating Surveys in RKStudios

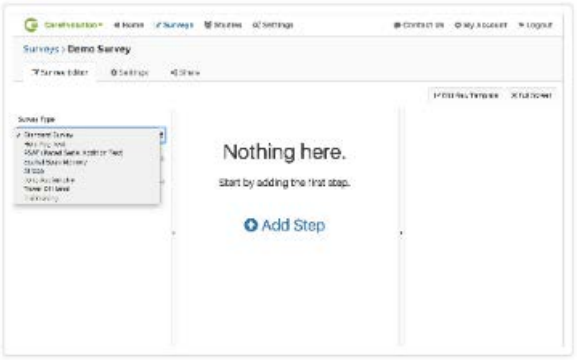
- Link to RKStudios Support Page for surveys: https://rkstudio-support.careevolution.com/hc/en-us/categories/360001623854-Surveys

1. Start by navigating to either the home screen or the surveys screen. Enter a survey name where it says "New Survey Name" and click "Add Survey." You

will arrive at the survey editor where you can begin creating the survey content.

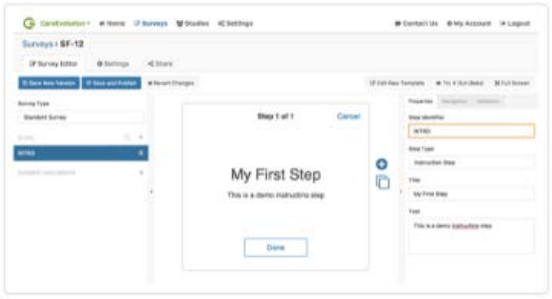


2. The first thing you may see when setting up a new survey is the survey type drop-down on the top left of the editor. Most surveys that you will create will probably be “Standard Surveys,” but, in some cases, you may also want to deliver an active task.

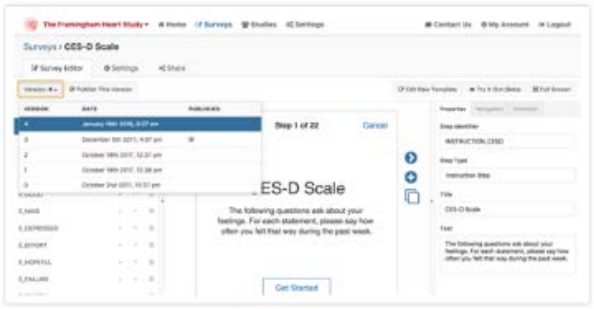


3. Surveys are simply a series of steps that are presented to the user. By default, they are presented in sequential order, but you can add branching rules to skip steps depending on the participant’s answers. If you are creating a standard survey, begin by clicking “Add Step” to add a step to your survey. Select “Step Type” on the right to select from question steps, instruction steps, consent steps, and more. For each question in a question or form step, RKStudio supports various answer formats. When you make changes to the step properties on the right, you will see the changes immediately reflected in

the preview view in the middle of the screen. You can also try out your survey via the RKStudio Review app to review it on a mobile device.



4. After you have added a few steps to your survey, you can save your survey via the "Save New Version" button at the top. You should save frequently to avoid losing your work. Survey content is versioned, so saving your survey simply saves a new version of it. You can always revert to a previous version of the survey by clicking on the version drop-down.



5. Before a survey can be included in a project, it must be published. You can publish a survey by clicking the "Publish This Version" button at the top, or "Save and Publish" if you would like to immediately publish your current changes. Publishing a survey version will make it the version that is given to the participant if they begin taking the survey in the MyDataHelps. This allows you to make changes to the survey that take effect immediately, even for participants to whom the survey has already been delivered. Note that this will have no effect on participants who have already finished taking the survey. Before you publish a survey that will go out to participants, you can test it via the RKStudioReview, app, which allows you to try out all versions of your surveys.

- <u>Here are some common questions and troubleshooting processes:</u>
    - **I have received messages that you have not been receiving my step or watch data and I have been participating.**

- First, find this participant in RKStudios by following these directions: after logging in to RKStudios → click on "Projects" → Offspring → Participants → type the name of the participant into the search bar at the top → click on the correct participant to open their account → Open "Apple Health Kit". Here you will see a list of data received from the participant's phone; this will include BP, HR, Stand hours, etc. Underneath each category you will see a date and time that it was received.
    - If that date is recent, then we are currently receiving data from their phone. They received a message stating otherwise because it had been over a week since the last time they opened their MyDataHelps App. Please remind this participant that they should be opening the app on their phone at least once per week (not simply leaving it running all the time, but actually tapping on the icon to load the app).
    - If the date is not recent; have the participant open their MyDataHelps app; they must be logged in to the app in order for us to receive. If they are logged out, please have them log back in. If they forgot their password, they can reset it by tapping on "Forgotten Password".
        - If the participant is logged in, have them open "settings" on their phone → scroll down and tap on "Privacy" → "Health" → "MyDataHelps", Here the participant should see a list of health categories (about 12) they should all be green (in order for us to receive data, the categories must all be on, if they are not, we will not receive that data from the participants phone). Now tap on "< Health" in the top left corner to go back, here look for Health Mate. If the participant sees Health Mate in this list, have them tap on it and turn all the categories on again. If Health Mate is not in this list, then → Have the participant open the Health Mate App → tap on "Profile" on the bottom tool bar → Scroll down to the sections titled "Apps" and Tap on "Health" here, the participant will receive a pop-up asking for permission to access health categories → have them tap on "Turn all categories on" and then "Allow".
        - If all the categories are turned on but the data is still not coming through to us, have the participant delete the MyDataHelps app and reinstall it. Once it has downloaded again, have the participants click on "login" in the top right-hand corner of the screen. They will enter their e-mail/phone number

and password. When the health access screen pops up, make sure they turn all categories on. Their data should appear in a few minutes. Sometimes if someone gets a new phone, or the IOS is updated it makes the data not come through to us.

XI. Weekly Meetings

- Currently weekly eFHS meetings are held (via zoom), as follows:
    1. Tuesday afternoon every other week from 4pm-5pm
    2. Wednesday Morning 9:00am-10am

- This meeting schedule may change as the project evolves, keep up to date with Dr. Murabito to know which calls you are expected to be present for.
- Minutes will be taken on both eFHS meetings by the eFHS coordinator

XII. eFHS Email Account

- The eFHS email account manages all eFHS weekly meetings as well as any of [redacted] regularly scheduled meetings
- The coordinator of eFHS will have access to the email [redacted].

XIII. 1 week follow up calls

- To ensure that participants are having no tech problems or any other problems with the MyDataHelps app, the 1 week follow up calls are implemented on all participants.
- All participants will receive a call one week after their enrollment date to check in.
- When enrolling the participant please ask them what day and time would be best for this call.
- The calls will be logged in the 1 week follow up document in the K drive located under K>eFHS>Heather>Offspring App> K-1wk follow up and mars question script
- 4 different tabs exist in this document in regards to 1 week follow up calls:
    1. “Completed registration and some surveys”
    2. “Registered but no surveys”
    3. “Incomplete registration”
    4. “Script”
- Please follow the scripts in the “script” tab when calling participants

XIV. Connectivity Protocol

- When a participant in RK studios has not had step data in 7 days or apple watch stand data in 7 days, the coordinator for eFHS will call the participant for a connectivity call to try and troubleshoot the issue
- RK Studios contains a segment “more than 7 days since steps” under the participants tab in the Offspring project where the coordinator can see these ID’s
- Rk Studios also contains a segment of “has watch” where the coordinator can see the last stand hour for those with an apple watch to determine which participants need to be called
- Please follow the connectivity protocol for eFHS located in K>eFHS>Heather>Offspring App>Protocols> Connectivity Protocol for further instruction on the monthly heat map that is provided by Care Evolution

XV. eFHS Call Log

- Whenever a participant calls or emails with a question pertaining to eFHS please log the call in the eFHS call log
- The call log is located in REDCap under “My Projects” , then project title “eFHS Call Log for Offspring Exam 10”
- Please ask Hongshan Liu for access to this page.

XVI. Participant Tracking System

- To look up a participant’s phone number, address or e-mail, login to PTS. You can enter their FHS ID or first and last name
- You will also want to keep log when you call a participant in PTS: to do this click on the participant you called→ contact log→ new record→ study will be eFHS which is number 13→ how you contacted them→ and the outcome of the call

BOSTON UNIVERSITY MEDICAL CAMPUS & BOSTON MEDICAL CENTER

RESEARCH CONSENT TO PARTICIPATE in the Electronic Framingham Heart Study (eFHS)

Title of Project: eFHS: eHealth, Mobile Technology and Health in the Framingham Heart Study

IRB Number: H-36586

Principal Investigators: Joanne M. Murabito, MD, ScM
[redacted]
Framingham Heart Study
73 Mount Wayte Ave
Framingham, MA 01702
murabito@bu.edu

Tuhina Neogi, MD
[redacted]

Emelia J. Benjamin, MD, ScM
[redacted]

Study Phone Number: ([redacted]

eFHS is a medical research study led by Drs. Joanne M. Murabito, Tuhina Neogi and Emelia J. Benjamin. These physicians and the Framingham Heart Study staff are available to answer any questions you may have.

Research studies include only people who choose to take part. Please take your time to make your decision about participating, and discuss your decision with your family or friends if you wish. If you have any questions, please feel free to ask the researchers.

Why is this study being done?

The purpose of the eFHS study is to improve our understanding of health in older people and to find new ways of preventing disease. We will do this by creating questions that you can answer using our mobile app on your smartphone or via our online platform, both designed for participants of the Framingham Heart Study.

Am I eligible to participate in the study?

To participate, you must be a member of the Framingham Heart Study. In addition, you need to have an email account with access to a daily internet connection or a smartphone.

What will happen if I take part in the eFHS research study?

Surveys

If you agree to participate in eFHS, you will be asked to complete a series of surveys about your life and health using our specially designed App. The surveys will ask about such things as your level of pain, fatigue, mobility, sleep, mood, loneliness, cognition, physical activity, social support, as well as health events like hospitalizations and falls, if any. It will take you about 20-30 minutes to get started. Going forward, participation in the study, including use of devices, will take about 5-10 minutes, on average, per week.

You will be asked to update information on the eFHS surveys ranging from every two weeks to every four weeks, or as your health changes.

Health History Updates

We also will create a module within the App that will detect if you enter certain hospitals. Entering a hospital may trigger questions regarding why you were in the hospital. We will use this information to understand how your health changes over time.

Continuing Care Document

You may have access to your Continuing Care Document through your primary care physician's electronic health record. If so, you might be asked to obtain it for eFHS.

Other study activities

As an eFHS participant, you may be invited to participate in additional study activities, or "modules" of the eFHS. The modules may include invitations to use electronic health sensors that measure your physical activity and heart rhythm. There may be electronic health sensors that measure other aspects of health that become available as the study proceeds that you may be invited to participate in. Participation in additional study modules is optional. That is, you can still be an eFHS participant without participating in additional modules.

If you decide to participate in these additional modules the eFHS app can also pull information from electronic health sensors or apps that you may already be using. To allow for this information to be provided to us, you will need to link these other devices to your eFHS app on your smartphone or other smart devices.

You may also be invited to participate in Randomization controlled trials (RCTs) during your eFHS participation. These temporary sub-studies will separate participants into small groups that receive surveys and information at different schedules in order to meet study aims.

Reminders and study communications

When there is a study activity that we want you to complete or consider, we will contact you. The study will offer a variety of communication options that you can choose from.

How long will I be in the study?

We would like to keep track of your health status for as long as you remain in the study. Keeping in touch with you and checking on your health periodically will help us look at the impact of pain on health, compare the health of those with and without cardiovascular disease, and investigate brain health. We plan to contact you on a weekly basis while you are in the study, approximately six months and if you choose you may stay in the study beyond six months. We will generally contact you directly through the eFHS App.

Can I stop being in the study?

Yes. You can decide to stop at any time. We won't delete the information about you that we have already collected, but we will stop collecting any new eFHS information and will stop contacting you.

To stop participating in the study, please send an email to the study staff at: [redacted].

What side effects or risks can I expect from being in the study?

Although we will do our best to protect your study information (see below), there is still a very small risk of loss of privacy. There is a risk that participating in the study will make you want to access the healthcare system more often, which costs money. An abnormal reading on a sensor might prompt you to want to talk to your health care provider. Whereas there may be benefits to you from seeing your healthcare provider, there are also costs, and the eFHS will not pay for any of your medical care. You should not see your healthcare provider solely for the purpose of collecting data for the eFHS.

For more information about risks and side effects, please ask one of the researchers. You can reach the study coordinator at FHS@bu.edu, Dr. Joanne Murabito at murabito@bu.edu, Dr. Tuhina Neogi at tneogi@bu.edu or Dr. Emelia Benjamin at emelia@bu.edu Monday to Friday between 9 am and 5 pm. If you want to speak to someone not directly involved in the research study, please contact the Boston University Medical Campus Institutional Review Board at (617) 358-5372.

Are there benefits to taking part in the study?

You will not obtain any direct health benefits from participating in the study. We hope that society will benefit from your participation – by participating, you will help us contribute to a better understanding of heart disease and we may find better ways to predict, prevent, and treat heart disease.

Will I get advice about my health from the study?

No. We will not provide you with information about your heart disease or clinical interpretation of your data from the study. **eFHS is a research study and is not clinical care. We do not provide medical services.** Participation in the eFHS does not in any way substitute for professional medical advice, diagnosis, or treatment that your doctor or other healthcare provider may give you. Always ask the advice of your healthcare provider if you have any questions about a medical condition. Do not

disregard professional medical advice or delay in seeking care because of something you have read as part of the eFHS study. If you think you may have a medical emergency, please call your doctor or dial 911 immediately.

What other choices do I have if I do not take part in the eFHS study?

You are free to choose not to participate in the study. If you decide not to take part in this study, there will be no penalty to you.

How is my information protected?

We will do our best to make sure that the personal information we collect about you is kept private and secure. ***The eFHS will never sell, rent, or lease your contact information.*** If information from the eFHS study is published or presented at scientific meetings or shared with other researchers, your name and other personal identifiers will not be used. However, we cannot guarantee total privacy – your personal information may be given out if required by law (e.g., to prevent possible injury to yourself or others).

This study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. All studies funded by the National Institutes of Health that involve identifiable information are covered by a CoC**.** The CoC provides how we can share research information. Because we have a CoC, we cannot give out research information that may identify you to anyone that is not involved in the research except as we describe below. Even if someone tries to get your information in connection with a legal proceeding, we cannot give it to them. The CoC does not prevent you from sharing your own research information. If you agree to be in the study and sign this form, we will share information that may show your identity with the following groups of people:

- People who do the research or help oversee the research, including safety monitoring.
- People from Federal and state agencies who audit or review the research, as required by law. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health.

Your information will be transmitted and stored using very secure systems. We label your samples and information only with a code, and we keep the key to the code in a password protected database. Only approved staff will be given the password. **We use other safeguards at our facilities and for our information technology and systems to protect the privacy and security of your information.**

Once your personal health information is disclosed to others outside the Boston University School of Medicine, it may no longer be covered by federal privacy protection regulations. You can review the privacy policies of the CareEvolution (for study surveys) company here: https://rkstudio-customer-assets.s3.amazonaws.com/CareEvolution/PrivacyPolicy.pdf

What are the costs of taking part in the eFHS study?

You will not be charged to take part in the study. Some of the study components may result in the use of some cellular data.

Will I be paid for taking part in the eFHS study?

You will not be paid for taking part in the eFHS study.

What are my rights if I take part in the eFHS study?

Taking part in the eFHS study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you.

By consenting to be in this study you do not waive any of your legal rights. Consenting means that you have been given information about this study and that you agree to participate in the study.

If you do not agree to be in this study or if at any time you withdraw from this study you will not suffer any penalty or lose any benefits to which you are entitled. Your participation is completely up to you. Your decision will not affect your ability to get health care or payment for your health care. It will not affect your enrollment in any health plan or benefits you can get.

We will tell you about new information or changes in the study that may affect your willingness to continue in the study.

Who can answer my questions about the study?

You can contact eFHS staff through “Contact Us” section of the App or by emailing us directly at [redacted]

You may also call [redacted]. You will be talking to someone at the Boston Medical Center and Boston University Medical Campus IRB. The IRB is a group that helps monitor research. You should call or email the IRB if you want to find out about your rights as a research subject. You should also call or email if you want to talk to someone who is not part of the study about your questions, concerns, or problems.

CONSENT

You can access and print copies of the eFHS consent form whenever you like via the FHS website.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to be in this study, please select the button that says “agree”.

Thank you for enrolling in eFHS!

Below are some tips to help get you started!

Using the MyDataHelps App

Participating in Offspring/Omni 1 Study means doing a few things:

1. Completing any surveys on the "Tasks" tab by their due date
2. Review a summary of your activity under the "Dashboard" tab in the app

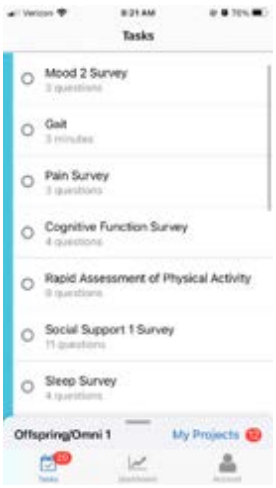
Below we will explain how the app works and how you can complete the above tasks.

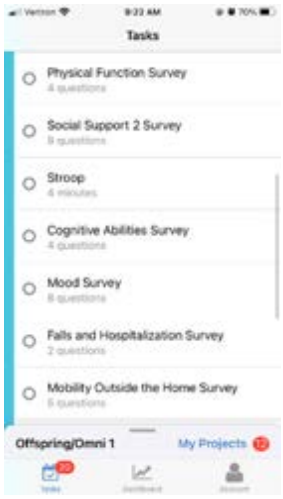
Surveys

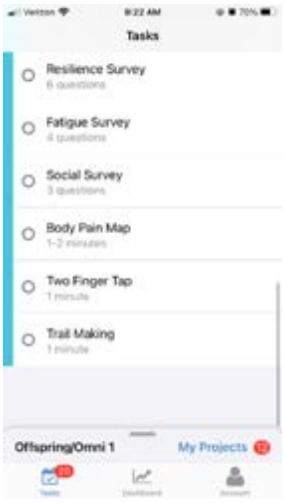
The first screen you will see upon logging into the app will be the list of surveys you have to complete. There are 21 total types of surveys that you will periodically be asked to complete in the MyDataHelps app. You will receive surveys every week, however not all 20 surveys will be delivered each week.

To complete a survey, please tap on the survey. You will then be given instructions on how to proceed.

The surveys will collect surveys about your life and health using our specially designed App. The surveys will ask about such things as your level of pain, fatigue, mobility, sleep and mood as well as health events like hospitalizations and falls, if any. We plan to contact you on a weekly basis while you are in the study, approximately six months and if you choose you may stay in the study beyond six months. We will generally contact you directly through the MyDataHelps App







Cognitive Tests: Trails, Stroop

The “Cognitive Tests” contain two tasks. In the trail making test, you will connect a series of labelled circles, in order. The time to complete the test is recorded. You will be asked to complete this survey every month. In the Stroop test, you are shown a series of words that are displayed in color and must select the first letter of the color’s name.

Tapping Speed

The “Tapping Speed” assessment will ask you to rapidly alternate between tapping two targets on the touch screen.

Gait

The “Gait” assessment asks you to walk for a short distance, which may be indoors. This task is to collect objective measurements that can be used to estimate stride length, smoothness, sway, and other aspects of your walking. Please use any assistive equipment you need to walk safely.

Pain Questionnaire

The “Pain Questionnaire” asks you about any pain you have experienced in the past 7 days and if it has interfered with any activities. This survey has 3 questions.

Body Pain Map Questionnaire

The “Body Pain Map Questionnaire” asks you about any persistent or recurrent pain that is present for the last three months. It then asks you to click on the Body Map where your chronic pain is located.

Physical Function Questionnaire

The “Physical Function” asks you about any difficulty you have performing a series of daily activities. This survey has 4 questions.

Sleep Questionnaire

The “Sleep Questionnaire” asks you about your quality of sleep over the past 7 days. This survey has 4 questions.

Mood Questionnaire

The “Mood Questionnaire” asks you about how you have felt in the last 7 days. This survey has 8 questions.

Mood 2 Questionnaire

The “Mood 2 Questionnaire” ask you about your feelings and how you have felt in the past week. This survey has 3 questions.

Fatigue Questionnaire

The “Fatigue Questionnaire” asks you about how you have felt in the last 7 days. This survey has 4 questions.

Social Questionnaire

The “Social Questionnaire” ask you about how you feel about different aspects of your life. This survey has 3 questions.

Physical Activity Questionnaire

The “Physical Activity Questionnaire” asks you about your physical activity within a typical week. It asks how often you engage in light, moderate or vigorous physical activities. This survey has 9 questions.

Mobility Outside the Home Questionnaire

The “Mobility Outside the Home Questionnaire” asks you whether you can get to rooms in your house other than where you sleep, areas outside your home, places in your neighborhood, places in in your town and places outside your town. It then asks how often you went to these places, if you needed aids or equipment and if you needed help from another person. This survey has 5 questions.

Fall and Hospitalization Questionnaire

The “Falls and Hospitalization Questionnaire” asks you if you had any falls in the past month and if you were hospitalized because of a fall. It then asks if you were hospitalized for a reason other than a fall. You will be asked to complete this survey every month. This survey has 2 questions.

Resilience Questionnaire

The “Resilience Questionnaire” asks you how respond to stressful events and difficult times. This survey has 6 questions.

Social Support 1 & 2 Questionnaire

The “Social Support 1 & 2 Questionnaire” asks about your social support and if you have help available to you when you need it. These surveys have a total of 19 questions.

Cognitive Abilities & Function Questionnaires

The “Cognitive Abilities & Function Questionnaires” ask you about how you have felt your brain has been working throughout the past week. These surveys both have 4 questions

FAQs

There is nothing left for me to complete on the “Tasks” tab. What now?

Keep the MyDataHelps app on your phone — it’s not done yet! The app will periodically have new surveys for you to complete.

What happens if I need to reinstall the MyDataHelps app, for instance if I have a new phone?

If for some reason you need to reinstall the MyDataHelps app, you do not need to go through registration again. Go through the steps to download the MyDataHelps app from the app store. When you open the app, you should see a button for “Log In” Tap this button to be taken to a login screen where you can enter your email and the password you created during registration.

What happens if I forget my password?

If you were to get a new phone or update the iOS software on your phone, you may find yourself back at the Welcome screen of the app.

If you no longer remember the password you made at the time of registration, the first thing you will do is tap the “Log In” button to be taken to the login screen. Then, enter your email before tapping the “Forgot Password?” button at the bottom of the login screen. You will be sent an email to reset your password. Follow the instructions in the email to enter a password. Once you have reset your password, you can go back to the MyDataHelps app and log in using your new password.

What are the requirements for running the eFHS app on my phone?

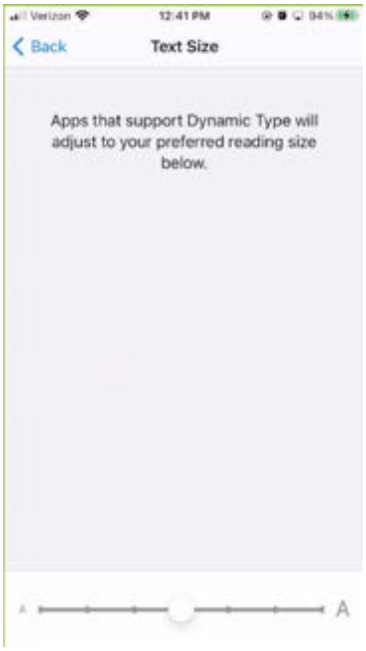
The MyDataHelps app is supported on iPhone, iPad, Apple Watch, and iPod touch running

iOS 10.0 or higher.

How do I adjust the text size of my screen?

To adjust the text size on your iPhone, first go to Settings on your phone. Once at Settings, scroll down to Display & Brightness and tap on it. Next, scroll down to Text Size and tap on it.

Now that you are at Text Size, drag the white circle at the bottom of your screen to adjust the text size. Dragging to the right makes it bigger and to the left makes it smaller.



Protocol Title: Early Pulmonary Fibrosis Detection in the Framingham Heart Study

Abbreviated Protocol Title: Early Pulmonary Fibrosis Detection

Identifying Words: Pulmonary fibrosis, screening

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Duration of Study: 4 Years in total (1 year per individual participant)
Number and Type of Subjects: 100 adult male and female subjects aged 50-85 years from the third generation and offspring cohorts of the Framingham Heart Study (FHS) without known interstitial lung disease (ILD).

Ionizing Radiation Use: Yes

Project Uses IND/IDE: No

Multi-Institutional Project: No

Investigator's Agreement

I have read the Early Pulmonary Fibrosis Detection in the Framingham Heart Study (FHS) protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator Date

Contents

A. Background

A1. Early Disease Detection for Pulmonary Fibrosis (PF):

While much work remains to be done, it is now apparent that **early disease detection for PF is achievable** in selected populations. For example, undiagnosed first-degree relatives of patients with pulmonary fibrosis (PF) (including those with sporadic Idiopathic Pulmonary Fibrosis (IPF) and familial PF[1]) are not only at an increased risk to develop PF but, are easily identified, are willing to participate in early detection studies, and, in some cases, may benefit by the early introduction of anti-fibrotic therapy.

In addition, it is becoming increasingly recognized[2-6] that early disease detection must play a central role if future progress is to be made in the care of those with, or at risk for, IPF. First, although nintedanib[7] and pirfenidone[8] can slow the rate of lung function decline in patients with IPF, the disease is relentlessly progressive and still carries a very high mortality rate.[9, 10] Thus, IPF patients have high unmet medical needs. Second, these IPF clinical trials required large sample sizes[7, 8] (in a disease reported to be relatively uncommon [occurring in ~0.5% of the population > age 65])[1,2,6] to achieve statistical significance. Future trials of novel therapeutics in patients with IPF, studied on the background of these therapies, will require even larger numbers of patients[3] or they may be of diminishing value. This looming problem in future IPF clinical trials has now been raised by many[2-6] **with growing calls for IPF trials to be more expansive and to include those the earliest stages of the disease**.[5, 6, 11, 12] Third, growing evidence from our group,[13-26] and others,[27-40] demonstrates that early/mild stages of undiagnosed PF frequently progress, can transition to radiologically identifiable IPF,[16, 17] and are associated with increased rates of mortality.[16, 17, 24, 32, 36, 40]

A2. The Burden of ILA: Beyond Clinically Identifiable IPF and Results of Early Detection:

Given the high unmet medical needs in patients with IPF, and the reported rarity of the disease,[41-43] it may have initially seemed logical that early disease detection efforts would have wanted to focus on a similarly prevalent group of people at risk to progress to clinically apparent IPF. Although our data demonstrates that interstitial lung abnormalities (ILA) are clearly a risk factor/precursor for IPF (identified near the time of death),[17] somewhat surprisingly our data,[13-26] and that of others,[27-40] demonstrates that clinically identifiable IPF appears to be only a small part of the burden of increased morbidity[16] and early mortality[16, 17, 24, 32, 40, 44] associated with a much more prevalent group with evidence for early/mild stages of undiagnosed PF. Evidence in support of this statement includes the following:

1) Imaging: While all prior studies show that ILA is much more common than IPF,[13-17, 26-31] even chest computed tomography (CT) patterns of usual interstitial pneumonia ([UIP], considered to be diagnostic for IPF),[45] and possible UIP (an imaging finding responsive to anti-fibrotic therapy[11] and reported to be consistent with UIP in up to 94% of cases[46, 47]) are more prevalent in the general population (0.2-0.4% [>age 50], and 4-5% respectively, Table 1) than would be expected given reported IPF prevalence rates.

2) Histopathology: In our recent publication on the histopathologic findings of ILA in the context of a lung nodule resection we demonstrated that, even though ILA were not specifically sampled, in pathologic specimens adjacent to a lung nodule, those with subpleural ILA had increased rates of fibrosis overall (in 82%), subpleural fibrosis specifically (in 52%), as well as increased rates of

fibroblastic foci (in 30%) and in some cases UIP (in 9%).[22] Consistent with possibility that some of these samples may represent early
stages of PF, many of these histopathologic samples meet 1 or 2 of the 3 definitions of UIP (patchy interstitial fibrosis, and fibroblastic foci) while end-stage lung findings (honeycombing) are rarer.[48]

3) Clinical Syndrome: Comparable to patients with IPF, research participants with ILA are older,[13, 14] have increased respiratory symptoms,[13, 14] reduced lung volumes,[13, 14, 27] exercise capacity,[26] and DLCO.[14, 28] More importantly, longitudinal studies demonstrate that there are consequences to developing ILA. For example, in a comparison of serial chest computed tomograms (CTs) over a 6-yr period in the FHS, imaging progression of ILA was noted in 6% of the population and was associated with an ~2-fold increase in the rate of FVC decline and an ~3-fold increase in the rate of mortality.[16] In 4 unique populations, ILA were associated with an increased risk of death that was not explained by age, smoking, measures of emphysema, coronary artery disease, or cancer.[17] In the Age, Gene/Environment Susceptibility–Reykjavik Study (AGES) the increase risk of death could only be explained by an increase in the rate of respiratory failure, in general, and PF, specifically (despite the fact that <7% carried a clinical diagnosis of PF prior to death).[17]

4) Genetic Studies and Biomarkers: Comparable to patients with IPF, research participants with ILA (particularly those on the UIP imaging spectrum) also have an increased prevalence of the *mucin 5B* (*MUC5B)* promoter variant,[14, 16, 23] as well as other genetic findings associated with IPF (see A.3.) and an elevation of biomarkers of that have been associated with IPF and fibrosis in general (e.g. matrix metalloproteinase 7 [MMP-7] and galectin-3).[32, 33, 49]

5) Early Disease Detection in 1st Degree Relatives: As noted in A.1. we have demonstrated that both early stages of PF, and more advanced stages of undiagnosed PF (including IPF and FPF), can be detected at a relatively high prevalence in undiagnosed 1st degree relatives of patients with PF.

These findings demonstrate that the burden of early PF extends beyond the reported prevalence of IPF. However, the measurable characteristics of those with early progressive PF at the greatest risk to experience adverse outcomes in additional specifically defined populations (who may be likely to participate in further early detection studies)[50, 51] has not been well described.

A.3: Critical Barriers:

First, despite the grave prognosis,[9, 10] a lack of effective medical therapy[9, 52] had contributed to a limited enthusiasm for diagnosing IPF at an early stage. However, now that nintedanib[7] and pirfenidone[8] have been demonstrated to reduce the rate of decline in lung function in patients with IPF (even when started early in the course of disease[53, 54] and in those with a possible UIP pattern[11] [the most common imaging finding in those with ILA[23]), limited enthusiasm has been replaced with mainstream discussions about the central role that expanded inclusion and early disease detection will play in future clinical trials of PF.[55-58] Second, significant advances (many generated from the prior grant cycle of this application) have been made in the field of early detection for PF in general, and IPF specifically.[13-40] As an example, our work in the FHS has demonstrated that an accelerated decline in measures of forced vital capacity (FVC, a hallmark of IPF severity)[59] first occurs in those with ILA in the interval when the imaging abnormalities are progressing.[16] This suggests that interventions, targeted to those with early evidence for PF, could help to prevent the initial losses of lung function that are a hallmark of this progressive disease. Finally, the discrepancy between the prevalence of ILA[13, 14, 17] and the reported prevalence of IPF,[41-43] had raised doubts by some about the clinical importance of early disease detection for PF. Our recent findings in 1st degree relatives of patients with PF have now demonstrated that early disease detection is an achievable goal, that some groups are willing, and

want, to participate in early PF detection studies, and that undiagnosed stages of PF, are not that uncommon and can lead to the early clinical institution of anti-fibrotic therapy. While this work is beginning to demonstrate the value of screening in relatives of PF patients, our work in other specific populations clearly demonstrates that the burden of early stage PF is not limited to relatives of PF patients alone.[13, 14, 16, 17, 22, 23, 26, 44]

A3. Improvement in the Scientific Knowledge:
Improvement in the Scientific Knowledge: The completion of this proposal is designed to provide critical information on the follow-up of undiagnosed imaging abnormalities that may one form the foundation of future targeted early PF detection studies.

B. Study Objectives:

1. To determine if those with prior ILA will be more likely to eventually obtain a clinical diagnosis of an ILD or PF.
2. To determine if those with prior ILA will be more likely to have reduced lung volumes (defined by a FVC or total lung capacity [TLC] < 80% of predicted), or a reduced DLCO (diffuse capacity for carbon monoxide, defined by those with a DLCO <80% of predicted after adjusting for hemoglobin) thus demonstrating a likely clinical diagnosis of ILD/PF.

C. Study Design and Methods:

C.1. Inclusion/Exclusion Criteria:

C1.a. Inclusion/Exclusion Criteria for recruited FHS participants.

We will enroll 100 FHS participants meeting the following inclusion/exclusion criteria. Prior approval for this protocol has been obtained from the FHS executive committee after extensive review. Participants will be identified by FHS study members and will be selected from those meeting the following inclusion and exclusion criteria initially starting with those in the FHS "Third Generation" cohort and followed later by those in from the "Offspring" cohort to minimize overall study visit times.

Inclusion Criteria:

a. A member of the Framingham Heart Study's third generation or offspring studies. Participants recruited on the basis of having prior interstitial lung abnormalities will include those with subpleural interstitial lung abnormalities who were prior participants in the FHS multi-detector CT2 (MDCT2) study (ILA group). The controls (control group) will include Framingham Heart Study participants from the third generation or offspring study who had not previously participated in the MDCT2 study (to minimize radiation exposure).

b. age 50-85 years

c. willingness to commit to the study visits.

Exclusion Criteria:

a. Prior doctor's diagnosis of idiopathic interstitial pneumonia (IIP) or IPF.

b. Participants who are younger than 50 years of age, and older than 85 years of age, will also be excluded, based our prior published data which demonstrated that *MUC5B* variants were not helpful in detecting imaging abnormalities in participants <age 50[14] and from our experience in recruiting undiagnosed first-degree relatives of patients with IPF as part of our IRB approved Clinical Genetics and Screening Protocol (IRB approved at the BWH).

c. A history of uncontrolled anxiety, depression, suicidal ideation, or other psychiatric illness. Those well controlled on medication can participate.

d. A Hospital Anxiety and Depression Scale (HADS)[70] score above 14 on anxiety subscale or 16 on depression subscale

e. Participants identified by FHS team members felt to have already have extensive burdens of time or concurrent radiation exposure (e.g., those undergoing neurologic PET CT scans).

C2. Informed Consent:

A FHS study investigator or designee will obtain informed consent after detailed review of the consent form with the potential study participant. Consenting subjects will be screened at the initial visit based on predefined inclusion/exclusion criteria. The investigator or designee will conduct a comprehensive review of the study design, study visits, procedures, risks and benefits of the study.

C3. Study Assessments:

The descriptions apply to all subjects (patients and relatives) unless otherwise specified.

Description of Study Assessments:

History, Physical Exam and Vital Signs

A complete history and physical examination should be performed, including all body systems pertinent to the patient. Vital signs for this study protocol include heart rate, blood pressure and oxygen saturation.

<u>High resolution Computed Tomography Scans of the Chest (HRCT)</u>

To assess for eligibility, HRCT scans will be evaluated for evidence of pulmonary parenchymal architectural distortion.

All patients consenting to a chest CT scan will undergo single prone volumetric thoracic chest CT scans performed at full inspiration using a Siemens Senstation-64 scanner, at baseline. The acquisition protocol is as follows: 120kVp, 200mAs, and 0.5s rotation time with reconstruction using a B31f algorithm at 0.625 (Sensation-16) or 0.75mm slice thickness & 0.5mm intervals with a 50cm field of view.

Chest CT images will be collected on hard-drives in DICOM format. Images will be loaded onto AZE VirtualPlace workstations (AZE Inc., Tokyo, Japan) (a high-throughput imaging system with up to 20 terabyte storage capacity that we have used in prior publications)[14] which help to maintain data security and confidentiality. In addition to being password-protected computer servers, these systems are housed an ID protected building, in locked room, and have no internet connection or connection to the Brigham and Women's Hospital (BWH) hospital information system. CT images in all subjects will be identified by unique study identifiers only.

All CTs will be evaluated by three readers blinded to any other interpretation. Final scores will be determined by a consensus of the three blinded reads. We define ILA as nondependent changes on chest CT affecting >5% of any lung zone including nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis[71, 72] in subjects who were either asymptomatic or who had not been previously diagnosed with ILD.[13, 14, 25, 26] Indeterminate scans will be defined as focal or unilateral ground-glass attenuation, focal or unilateral reticulation, and patchy ground-glass abnormalities (<5% of the lung). Next, to provide further detail on the radiologic characteristics of ILA we will create additional ILA subsets further defined by those with or without pulmonary parenchymal architectural distortion highly suggestive of a fibrotic lung disease (Definite Fibrosis)[14, 73] and a subset defined by having either a definite usual interstitial pneumonia pattern (UIP Pattern), a possible UIP pattern, or pattern not consistent with UIP.[48]

Review of Available Pathology

Surgical lung biopsy (SLB), if performed, will be assessed for histopathologic evidence of an IIP. The pathology slides will be adjudicated by a Chest Pathologist at BWH.

Pulmonary Function Testing

All equipment, procedures, and personnel qualifications for the assessment of lung function are based on the recommendations of the American Thoracic Society (ATS 2005) and will be performed and interpreted in accordance with published guidelines [74]:

Spirometry measurements will include FVC and forced expiratory volume in 1 second (FEV_1).

DL_{CO} will be measured by determining the diffusing capacity of the lung for carbon monoxide.

Questionnaires:

St. George's Respiratory Questionnaire-for IPF (SGRQ-I)

The SGRQ-I is version of the St. George's Respiratory Questionnaire modified and validated (PMID: 20861296) to measure impact on overall health, daily life, and perceived well-being in patients with idiopathic pulmonary fibrosis.

Herlihy Registry Questionnaire

The Herlihy registry allows subjects with interstitial lung disease to provide blood samples for the ILD Program's tissue repository and to complete an online questionnaire. The questionnaire addresses questions related to medical history, medication history, and lifestyle. The questionnaire also asks about symptoms of lung disease, shortness of breath, family history, medical conditions, and health-related quality of life. This registry is available to investigators to pursue clinical and translational research related to Idiopathic Pulmonary fibrosis, autoimmune lung disease, and other forms of interstitial lung disease.

The Hospital Anxiety and Depression Scale (HADS)

After each follow-up survey, the study staff will immediately review the scales assessing depression and anxiety (The Hospital Anxiety and Depression Scale (HADS)). Should a relative score above our pre-specified cut-off score for this scale, the study staff will alert the PI. The project coordinator will call the patient after the visit, review the elevated score with the patient and ask questions to monitor the safety and well-being of the patient. The project coordinator will document this conversation [**see attached Safety Monitoring Note**] and review the case with the PI. The PI will make appropriate referrals to the patient's primary care physician and/or a mental health professional as needed. All cases of safety monitoring will be reviewed by the IRB and our panel of co-investigators according to our AE reporting protocol [see attached AE reporting schema].

Attitudes about the Study

A questionnaire measuring the attitudes towards, and the impacts of, receiving information and being part of the study. To measure this, all participating relatives will complete a **baseline and a follow-up survey after 6 months** that have been used for identical purposes at the Brigham and Women's Hospital for the MedSeq Project [PubMed IDs: 24645908, 26479555].

Gastroesophageal reflux disease (GERD) questionnaire

The GERD questionnaire is a 6-item, easy to use questionnaire that was developed primarily as a diagnostic tool for gastroesophageal reflux disease in primary care.

Laboratory Assessments (8.5 ml PAXgene tube, 10 ml EDTA tube, and 10 ml serum separator tube):

Routine Clinical Laboratory Tests

- Hematology (complete blood count with platelet count and automated differential)

- Serum chemistry profile (alkaline phosphatase, ALT/SGPT, AST/SGOT, direct bilirubin, total bilirubin, anti-CCP antibody, anti Scl-70 antibody, antinuclear antibody)

Telomere Length Testing:
De-identified blood samples will be sent to Dr. Geraldine Aubert, our collaborator at Repeat Diagnostics, Inc. (Vancouver, Canada), for 6-panel Flow-FISH based telomere length. Repeat Diagnostics performs the majority of clinical telomere testing in North America. The assay utilizes multicolor Flow-FISH on 6 subsets of human leukocytes: granulocytes, total lymphocytes, B-cells, naive T-cells, memory T-cells and NK cells. Telomere length is determined by flow cytometry, by comparing native cellular fluorescence to the fluorescence of cells stained with DNA dye LDS751. 6 panel testing has superior sensitivity over 2-panel (granulocyte & total lymphocyte) testing, as mosaicism and cell-specific short telomere lengths are commonly observed in patients with confirmed short telomere syndrome (STS).[75] Lengths are reported in absolute kilobases and as age-adjusted percentile of the population distribution.

VISIT 1

STUDY COMPONENT	Time	Radiation
CONSENT FORM	20 minutes	
MEDICAL HISTORY AND PHYSICAL EXAM	30 minutes	
CHEST CT SCAN	10 minutes	5.8 mSv
PFT	40 minutes	
SIX MINUTE WALK TEST	15 minutes	
BLOOD COLLECTION	10 minutes	
QUESTIONNAIRES	60 minutes	
VISIT 2		
DISCLOSURE	60 minutes	
VISIT 3		
MEDICAL HISTORY AND PHYSICAL EXAM	30 minutes	
PFT	40 minutes	
6 MINUTE WALK TEST	15 minutes	
QUESTIONNAIRES	60 minutes	

Study Visit Windows:

Data will be collected yearly, allowing +/- 28 days.

Informed consent will be obtained prior to review of any clinical information for the purpose of this research study.

Data Collection:

FHS participants will be identified by FHS study personal from Boston University Medical Campus and approached by phone for participation in this study. Informed consent will be obtained prior to initiation of any study procedures.

Screening (Visit 1, Day 0):

The following testing will be performed at the screening visit:

- Informed consent
- Full medical history
- Full physical exam
- Questionnaires
- Six-minute walk test
- Chest CT scan
- Spirometry, DLCO
- Clinical Laboratories
- Telomere Length Testing

Visit 2 (Day 1 – 180):

Within 6 months of screening, relatives of subjects with IIP will be offered a follow up visit to disclose the results of genetic and phenotypic testing. This visit will include:

- Review of results of CT, pulmonary function testing, and laboratory testing.
- Subjects with evidence for either an IPF pattern on Chest CT imaging or with evidence for imaging changes suggestive of an early stage of pulmonary fibrosis and with significant evidence for progression with repeat testing, will be offered a referral in our ILD clinic for a clinical evaluation and a consideration for further management. In addition, if any incidental findings are discovered on chest CT imaging or other clinical or laboratory tests, we will disclose this information to the subject and will request permission to share this information with the subject's primary physician.
- If some of the results are not available at the time of the Visit 2, we will offer the patient: an extra-visit, a video conference or phone call, to communicate the remaining results. The video conference will be conducted using a partners-approved video platform.

Visit 3 (Day 365)

The following testing will be performed at the Visit 3:

- Brief medical history
- Spirometry, DLCO
- Six-minute walk test
- Questionnaires

Study Visits for FHS Participants:

Table 6. Study Assessments for FHS Participants	Visit 1	Visit 2	Visit 3
	Day 0	Day 1 - 180	Day 365
Informed Consent	X		
Vital Signs	X		X
Full History and Physical Exam	X		
Brief History and Physical Exam			X
Questionnaires	X	X	X
Spirometry, DLCO	X		X
Six Minute Walk	X		X
Chest CT	X		
Clinical Laboratory Testing	X		
Telomere Length Testing	X		
Review of Test Results		X	

C4. Risks and Discomforts:

Risks of Lung Function Tests:

- Cough
- Lightheadedness
- Discomfort due to technique
- Shortness of breath
- Fatigue

Lung function tests will be performed by a qualified member of the research team and in accordance with published guidelines.

Risk of Questionnaires:

- Fatigue
- Distress related to questions

Risks of Blood Draws:

- Bruising
- Pain
- Infection
- Lightheadedness, and/or fainting

Specimens will be collected by a qualified member of the research team at the time of the study visit and drawn according to institutional standards.

Risks of Six Minute Walk Test:

- Discomfort due to technique
- Shortness of breath
- Chest tightness
- Abnormal blood pressure
- Fainting
- Arrhythmia
- Heart attack
- Fatigue

Six-minute walk tests will be performed in accordance with published guidelines. Patients will be monitored by a respiratory therapist throughout the test.

Risks of Radiation Exposure:

- Discomfort due to technique
- The radiation exposure at doses associated with this study slightly increase in the risk of developing cancer later in life.

Any additional blood samples will be sent for storage to the Framingham Heart Study. We do not think that there will be further risks to subject privacy and confidentiality by sharing samples with collaborators outside Partners. However, we cannot predict how information will be used in the future. The samples and data will be sent with the only the subject code number attached. Subject name or other directly identifiable information will not be given to central banks. There are many safeguards in place to protect subject information and samples while they are stored in repositories and used for research.

C5. Methods and Procedures:

All study procedures will be performed in accordance with accepted standards of practice. Relevant changes in clinical status and medication use, symptom history and adverse events will be reviewed at each study visit.

Blood samples will be obtained via a single phlebotomy encounter at each study visit. Clinical testing will be performed at BWH in the LMM.

Pulmonary function testing and six-minute walk testing will be performed in the Pulmonary Function Testing Lab at BWH and reported in accordance with ATS guidelines. The SGRQ will also be administered and scored in accordance with published guidelines.

Information on hospitalization and IPF exacerbations will be obtained via direct patient interviews and medical record review. Mortality data will be collected from review of our hospital database as well as the Social Security Death Index.

D. Study Endpoints

The primary study endpoints will be to:

a. To determine if research participants with prior evidence for ILA (ILA group) will be more likely to have preclinical pulmonary fibrosis (as determined by a chest CT imaging characteristic and evidence for FVC/TLC/DLCO < 80% of predicted).

b. To compare the psychosocial stress of testing in those identified as having preclinical PF compared to those who do not have preclinical PF.

Secondary study endpoints will include:

a. Assessment of the prevalence of clinically relevant mutations (*MUC5B* variant (rs35705950), telomere complex mutations or other) in those with abnormal imaging (based on prior genetic results from the FHS).
b. Determination of distinguishing baseline clinical, radiographic or physiologic characteristics that reliably differentiate patients with short telomeres (and thus should be screened for STS) from those who do not.
c. Annual rates of decline in measures of pulmonary function, 6MW distance and DLCO
d. Frequency of $\geq$10% reduction in FVC or $\geq$15% reduction in DLCO

D2. Recruitment

Prior MDCT2 participants with ILA (ILA group) from offspring and gen 3 still alive between ages 50-85. Total number of prior ILA cases - goal to recruit ~20-25 for follow-up of ILA and 75-80 matched controls **(**control group), who did not previously participate in the MDCT2 study to minimize radiation exposure). FHS participants meeting current enrollment criteria will be identified by George O'Connor and his group of FHS investigators as BU. This study will employ Maureen Valentio (or another designee identified by FHS investigators) who is an active clinical coordinator at BU will help to recruit FHS participants in conjunction with the 10th examination (from the FHS Offspring Cohort). All participants will be given the option to opt out of chest CT imaging (although they will be informed that the study may be of less value without this important piece of data). For the 20-25 FHS participants with prior ILA on their MDCT2 imaging (ILA group) we will forgo chest CT characterization if they have had a subsequent chest CT image obtained as the result of incidental findings noted on their prior MDCT2 image or if they have had another clinically obtained chest CT subsequent to their MDCT2 image (we will request the participants provide a copy of this chest CT for evaluation). For the 75-80 FHS participants who did not previously participate in the MDCT2 study (control group) we will forgo chest CT characterization if they have had a clinically obtained chest CT within the last five years (and we will request the participants to provide a copy of this chest CT for evaluation). If a participant obtains a chest CT, we plan to use a lower dose protocol (already approved for a similar screening study by the Brigham and Women's Hospital IRB) include a single prone inspiration chest CT image that would result in 5.8 millisieverts of radiation exposure. For comparison everyone receives radiation exposure from natural background sources from the earth and sky. This dose of radiation would be the same as a person would normally receive in 1.88 years from natural sources.

Our clinical investigators adhere to clinical research policies put forth by several regulatory bodies. These bodies include FDA, DHHS and the Massachusetts Board of Registration in Medicine. Our physicians also follow Good Clinical Practice, OSHA and Policies set forth by the Partners IRB, the BWH and Harvard Medical School, in addition to principles of practice associated with medical Oath.

Risks to subjects are minimized by careful screening of subjects and disqualifications of subjects meeting exclusion criteria, with a special emphasis placed on excluding relatives from participation if they are at high risk of psychological stress related to the disclosure of test results (as measured using the MADS scoring system and a history of mental illness or severe anxiety). Subjects are monitored throughout the study assessing adverse events with assessment of physical exam and vital signs. All procedures in this study are consistent with sound research design.

D4. Dataset Management, Sample Tracking and Processing

We will use existing bioinformatics support for computer-generated subject identification numbers (IDs). The CDNMs LIMS system utilizes two applications for sample tracking and processing: a commercial system, LabVantage™ LIMS (http://www.labvantage.com) and an internally-developed electronic Project Management Pipeline (ePMP). LabVantage™ LIMS enables centralized biological specimen tracking to comply with Good Laboratory Practices (GLPs) & Good Clinical Practices (GCPs), satisfies patient consent requirements (HIPAA), enhances scientific accuracy and improves development efficiency. This LIMS has intricate chain-of-custody functionality, including detailed location management, aliquot/derivative and pooled sample tracking and electronic signature captured transfer and disposition. These features will be essential data tracking variables required in the performance of both our clinical and radiologic projects. Project Management Pipeline (ePMP) is an application shared between research and laboratory staff. All information will be collected in a HIPAA compliant fashion and will be stored on password-protected computer servers. Only the research coordinators and PIs of this proposal will have access to protected patient specific health data, all other analyses will be performed on de-identified datasets.

D4. Confidentiality and HIPAA Considerations

All subjects must provide written informed consent and signed HIPAA authorization prior to the performance of any screening or main study procedures. Subject confidentiality will be protected throughout the study and no subject-identifying information will be released to anyone outside the project. Confidentiality will be secured through several mechanisms. Each subject will be assigned an anonymous study ID, which will be used on all study forms. Any study forms and paper records containing personal identifier information (e.g., address, phone number) will be kept secured and locked. No personal identifiers will be placed on biological samples and other documents forwarded to central labs and reading centers.

Access to all subject data and information, including biological samples, will be restricted to authorized personnel. Only authorized personnel will have access to study data files. Authorized personnel will be assigned user logon IDs, passwords and appropriate access privileges to study data. Study subjects will be identified only by their initials and subject ID number. No personal identifiers, such as name,

address, social security number will be entered into the study database. Any subject-specific data reported to any study committees will only be identified by subject ID number.
Finally, subjects will not be identified by name in any reports or publications, nor will the data be presented in such a way that the identity of individual subjects can be inferred. Analysis files created for further study by the scientific community will have no subject identifiers.

HIPAA Considerations
Prior to enrolling subjects, you must obtain subject authorization. The elements of authorization include:

- Who may use or disclose the information?
- Who may receive the information?
- Purpose of the use or disclosure
- Expiration date of event (not sure I understand this?)
- Individual's signature and date
- Right to revoke authorization
- Right to refuse to sign authorization
- A statement about the potential for the personal health information (PHI) to be redisclosed by the recipient

The authorization can be a separate document or may be combined with the consent form. The participant or participant's legally authorized representative has the right to revoke the authorization in writing, at any time.

HIPAA compliance is the responsibility of the study principal investigators.

E. Data analysis

E1. Analysis Plan and power calculations.

With a follow-up of 20-25 participants with ILA (**ILA group**), the standard error of the mean when estimating the proportion of participants who will progress is about 9%. So, if we observe that 40% of the participants have progression (prior data demonstrates progression in ~40-60% see ref 4), the CI for that estimate will be about 22% to 58%. Although statistics are important, part if this aim is designed to identify early cases of pulmonary fibrosis who warrant further clinical evaluation (and in some cases deserve to be started on anti-fibrotic therapy). The raw numbers of cases we identify here will be of great importance to the NHLBI and reviewers as it would assess the potential value of (percentage of those identified) further screening in those who have been identified to have had an abnormal chest CT. This study would lay the foundation for larger proposals designed identify those with prior imaging evidence for ILA that have the greatest risk to progress to active disease. It would also provide significant guidance to the standardization and likely outcomes associated with ILA when identified as an incidental finding in the general population.

We will perform a longitudinal analysis comparing repeated measures of the difference (e.g., in HADS score) between those who choose to, and those who choose not to, receive their genetic testing

results. In addition to unadjusted analyses, we will perform analyses adjusting for baseline demographics (e.g., age) and the baseline scores (recorded at the initial visit).

References:

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Framingham Heart Study

Manual of Operating Procedures

SOP-version 0.1

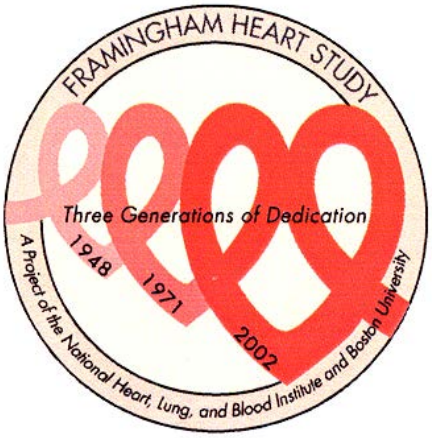
August 11, 2020

Maureen Valentino
Emily Manders
Ogechi Nna

Televisit Protocol

Offspring Exam 10, Omni 1 Exam 5

June 1, 2020 – August 31, 2021



Tracking of Revisions to this FHS Protocol SOP

Revised Section	Revision Author	Date (s) of Revisions; source	Approved by, Date	Revisions	Previous Pages #s section changed	Distribution Date

Table of Contents

A. Rationale for Televisit

The world-wide pandemic of COVID-19 forced the suspension of the Framingham Heart Study (FHS) in-person exam on March 12, 2020. In order to continue the exam with the Offspring and Omni 1, we have proposed and received permission to perform televisits with these cohorts. The televisits will be administered by staff from the Recruitment team (consent and tracking), Exam team Nurse Practitioners (NP) to administer the Medical History (minus blood pressure and ECG) and the Exam team Technicians to administer the Technician (minus MMSE) and Self-Administered Questionnaires (SA).

Performing these parts of the exam will be beneficial for two reasons:

- We will be able to reach those participants who would not come into the exam (due to distance, who do not feel safe to come in due to COVID or who have refused). This way we get a more detailed medical history than just a Medical History Update done by the HIM team.
- Participants that complete the Consent, Medical History and Questionnaires and want to come to FHS to complete the rest of the exam when we reopen, (which includes the Ancillary Studies), will be in the building for much less time (~ 2.5 hours instead of 4 hours), making it safer for our elderly participants and staff.

B. Supplies Needed

- Computer (laptop or desktop) connected to FHS via VPN (assumes not at FHS)
- Access to
    - PTS
    - FHS REDCap
    - Zoom
- Telephone (backup to "computer" audio)
- Technician Handouts

C. Exam Components

Section I: Informed Consent & Tracking Procedures

1) Informed Consent
2) Tracking Information Form

Section II: Tech-Administered Questionnaires

1) Physical Function
    a. KATZ-ADL Scale
    b. Rosow-Breslau
    c. NAGI
2) Depressive Symptoms
    a. CES-D

3) Physical Activity Questionnaire
    a. PASE
4) Other
    a. Fractures
    b. Sociodemographic Questionnaire
    c. Respiratory Disease Questionnaire

Section IV: NP-Administered Medical History

1) Medical History
2) Referral (if applicable)
3) Medical Portion Televisit Date

Section V: Self-Administered Questionnaires

1) General Information and Sociodemographics
2) Health Insurance and Medications
3) Health Survey (SF-12) Part 1
4) Health Survey (SF-12) Part 2
5) Bleeding History
6) Sleep Questionnaire
7) Cannabis Questionnaire

Section VII: Exam Completeness

1) Exam Technician Portion Televisit Date
2) Televisit Exit Interview

D. Step-by-Step Process

Summary of Steps to Complete All Televisit Components

1. Call 1: Recruit and schedule televisit calls
2. Mail materials to participant
3. Email 1: Reminder with Zoom link
4. Call 2: Set-up and consent
5. Email 2: Reminder with Zoom link
6. Call 3: Complete exam components
    a. NP administers Medical History
    b. Exam technician administers exam questionnaires

1. Call 1: Recruit Participant and Schedule Televisit Calls

1. The Recruiter will make the recruitment call: establish the electronic viability, type of equipment, browser, etc.
2. The appointment for the televisit with the NP is scheduled first, as that is approximately 1.5 hours long.

3. After scheduling the televisit, the Zoom set-up call is scheduled. Ideally it is made 48 hours prior to the televisit appointment. They will be sent an email with the Zoom meeting link the day before the set-up call.
4. The participant is instructed that they will receive the following in an email or by mail:
    a. A schedule of the appointments (2).
    b. The details about each appointment.
    c. The date the email Zoom link will be sent.
    d. A copy of the consent form.
5. Verify their email address.

2. Mail Materials to Participant

One to two days after the recruitment call, staff will mail an appointment letter that confirms all scheduled televisit dates and the study consent form, to the participant. A copy of the appointment confirmation letter is included in Appendix A.

3. Email 1: Reminder for Set-up Call and Televisit Consent

A reminder email will be sent to the scheduled participant the day before the Zoom set-up call. Instructions for the equipment the participant will use for the televisit will be attached. A copy of the email is contained in Appendix B.

4. Call 2: Zoom Set-up and Consent Administration

1. Ask the participant if they have had a chance to review the instructions. Ask them to open the email.
2. Use the instructions for the identified equipment being used by the participant (Appendix D-G.) Be certain the audio for the computer is working. Once computer audio is confirmed, the call can be ended.
3. In REDCap verify DOB on the **Participant Information Page**.
4. Save & Exit the Participant Information Page and go to the consent for Exam 10/5 in REDCap.
5. Administer the exam televisit econsent form in REDCap:
    a. Ask the participant if they have reviewed the consent.
    b. Share the screen in the Zoom function so that the participant is able to review the consent.
    c. Once the consent is reviewed, remain on page 10. Have the participant read each question on the consent form. Have the participant indicate the response to each question (yes or no) and click the designated answer.

d. Once this page is completed, proceed to page 11, the signature page. Enter the current date in the participant field and the researcher field and enter Technician ID number for administrator of consent.
e. Give the participant control of the remote and have the participant type their name or initials in the **consent comment box**.
f. Take back control of remote and proceed to page and have the participant read and ok the electronic certification box.

6. Review and update all the contact information on the PTS roster page.
7. Review and update ADMIT ALL form in REDCap.
8. Review time and content of televisit appointment with NP/Technician and tell them to expect an additional email Zoom invitation.
9. Remind the participant to end the Zoom meeting by clicking on the 'end meeting box' in the lower right-hand corner. Thank the participant and end the meeting.

5. Email 2: Reminder for Medical History and Questionnaires

The NP will send a reminder email the day before the scheduled appointment to complete the medical history and various questionnaires. A copy of the email is in Appendix C.

6. Call 3: Administer Exam Components

NP TELEVISIT CHECKLIST

- Have Daily or Weekly Schedule
- Know participants email and phone number
- Send Zoom email (using email template) via Outlook to participant and Technicianday before appointment. Bold date/time and Zoom link
- Have phone ready in case of computer malfunction
- Make sure VPN is working
- Have REDCap open to participant ID
- Before leaving Zoom, make Technician the Host
- Remember to fill out NP Portion Televisit Date in REDCap

a. NP-Administered Medical History

- Receive schedule from Recruiter, Barbara or Crystal Reports
- Decide which NP is working with participant
- Decide which Technician is working with participant
- Once Recruiter makes appointment, unless you hear appointment was cancelled or rescheduled, the appointment is on and send email Zoom link day before

- Day before appointment
    - Send template email letter with Zoom link to participant- Remove "Join by Sip" and below
    - Send Zoom link to Technician (for Outlook calendar)
- Day of appointment
    - Make sure VPN working and you have a quiet space to work
    - Have REDCap open on your screen
    - Have Medication template available (on screen or printed out)
    - Call participant to make sure they can access Zoom
    - Have phone available for backup/computer failure
    - Arrange with Technician when to join Zoom- by text or time
    - Verify participant name/DOB
    - Make Technician Host before leaving Zoom

EXAM TECHNICIAN TELEVISIT CHECKLIST

- Have Daily/Weekly Schedule
- Receive Zoom email on Outlook calendar from NP
- Make sure VPN is working
- Have REDCap and Handouts open before starting Questionnaires
- Make sure you are the Host before NP leaves in order to Screen Share with participant
- Complete all Questionnaires (except MMSE), including Self-Administered Questionnaires
- Do Televisit Exit for Feedback
- Read Disclaimer
- Complete Technician Portion Televisit Date in REDCap

b. Exam Technician-Administered Questionnaires

- Receive schedule from Recruiter, Barbara or Crystal Reports
- Day before appointment
    - Decide which Technician is working with participant
    - Receive Zoom link email from NP in Outlook
    - Arrange with NP when to join Zoom- by text or time
- Day of appointment
    - Make sure VPN working and you have a quiet space to work
    - Have REDCap open on screen
    - Have handouts readily available on screen
    - Have phone available for backup/computer failure
    - Log into Zoom per arrangement by NP

Appendix A: Recruitment Call Script and Appointment Letter

Recruitment Call Script

Hi this is _____ calling from the Heart Study. Is this _____

How are you? It looks like we may have previously spoken to you and you had indicated that you would not be able to attend the exam this year. The reason I am calling is the coronavirus/COVID-19 has given the Heart Study an opportunity to be more creative in how we collect data through a tele-exam. Have you heard of tele-exams? Yes/No

What we are hoping to do is a brief research exam with you using your computer, laptop, or tablet. Is this something you would be interested in?

No: Check if they need an MHU and end the call
Yes: Great! What type of computer do you have? (refer to flowchart)

Have you used Zoom? Yes/No

No: Zoom is a popular vehicle for conducting virtual meetings on a computer or device. This app allows people to see and hear each other. Many doctors' offices are currently using this platform of medical appointments. BU uses this platform because it is both, secure and one of the best products for this type of online visit. Would you like to give it a try? → go to set up

Yes: Great! I'll go over our set up and tele-exam-

Set up: We will schedule an appointment. The appointment will last approximately an hour and half. The tele-exam will consist of a very detailed health interview and some questionnaires about mood, physical activity and socio-demographics.

A few days before the appointment, I will send you a Zoom Link and I will call you a couple of days before your televisit. We will take this time make sure everything is working and guide you through installing and using Zoom. At this time, I will also administer consent and update your contact information. This should take no more 20 minutes.

What date and time would you like your televisit for?

What time on _____ (1-2 days before televisit) would you like me to call you so we can practice setting up the link and do the consent?
I will email you an appointment packet in the mail. It will include a letter summarizing our call, all the dates and instructions, a copy of the consent form for you to review prior to my call with you. **Do you have any questions?**

Ok so your tele-exam appointment will be on _____ and I will call you_____ to set up Zoom and complete the consent. This will be coming in writing as well when I send your appointment packet.

Thank you and have a great day

Appointment Letter

Dear [Participant],

Thank you for participating in the Framingham Heart Study. This is the schedule for your televisit with us on Wednesday, July 1, 2020 @ 1:00 pm.

Sunday, June 28, 2020: The link for the televisit will be sent in an email. Please look for this email and be sure to check your spam or junk mail if you don't see it in your inbox.

Monday, June 29, 2020: One of our staff will be calling you at **2:00 pm**. At this time, we will verify that your televisit link works, administer consent and update your contact information.

Wednesday, July 1, 2020 @ 1:00 pm: You will have your televisit with our staff. (You will receive an additional email with the link for this visit). **Please have your medication bottles ready**. This visit will be approximately 1 hour and 30 minutes.

Please read the enclosed/attached consent form before your televisit.

If you have any questions, please contact [redacted]

[redacted]

Daniel Levy, MD
Director, Framingham Heart Study

Appendix B: Email Reminder for Set-up and Televisit Consent

Hi _____,

Below is the link you need to click on to access our Zoom screen visit. I will call you at _____ a tomorrow to walk you through it, but it should be pretty easy! Just to remind you, tomorrow we will make sure the link works and we will go through the consent form. If you have a chance to read it before our call, that would be great. The remainder of your visit will occur on _____. The Nurse Practitioner will be asking questions regarding your health since _____. If you take any medications, please have them handy for review with Nurse Practitioner. After that that one of our techs will join and administer a series of questionnaires. The visit should last no more than 1.5 hours.

I look forward to SEEING you tomorrow at _____. If you have any questions you can reach me at 508-935-3417.

Best,

Maureen

TO JOIN MEETING:

[redacted]

Appendix C: Email Reminder for Medical History and Questionnaires

Dear [Participant],

Thanks so much for volunteering to complete our Medical Health Update and Questionnaires tomorrow, **Tuesday June 1 at 10:00 am**. I look forward to speaking with you then.
Please have your medications with you. We will also need to know about your health care visits (with date, name, and locations) since the FHS last connected with you on (date).
When I am done, the Technician will join us to ask you some Questionnaires.

At the time of our appointment, I will call you to help you connect to Zoom.

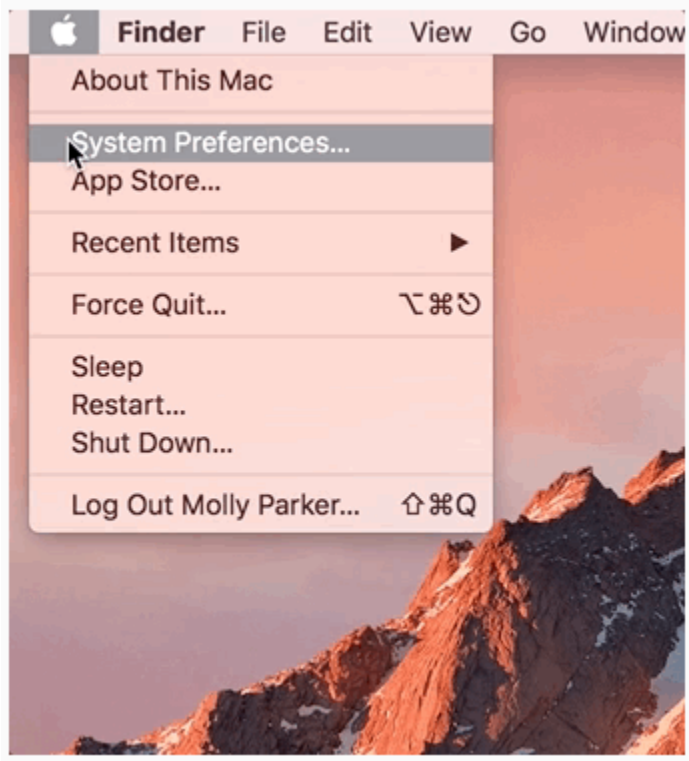
Thanks again,
[redacted]
Framingham Heart Study

TO JOIN MEETING:
[redacted]

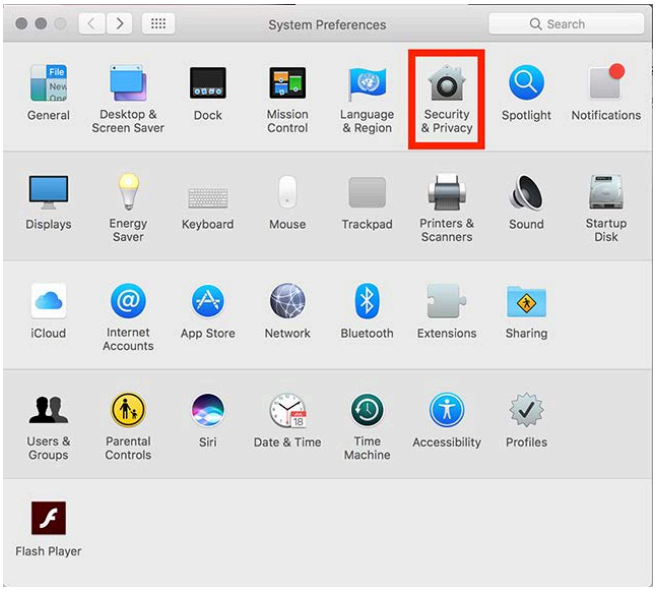
Appendix D: Zoom Instructions for Mac

DOWNLOADING ZOOM ON MAC AND ACCESSING ZOOM MEETING

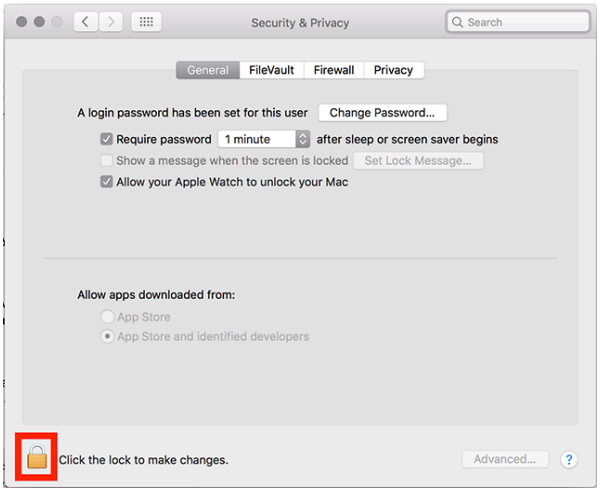
1. Click on 'System Preferences' under the Apple in the top left.



2. Click on 'Security & Privacy'.

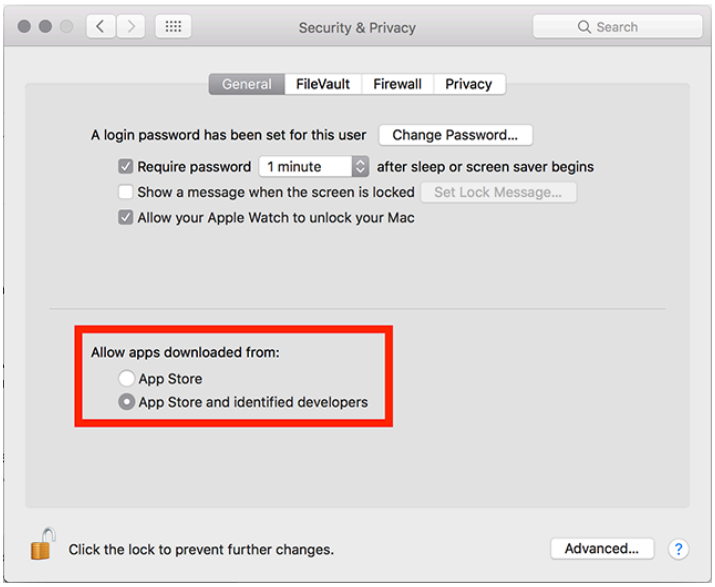


3. Click the ‘lock’ icon at the bottom left to have access to make changes.



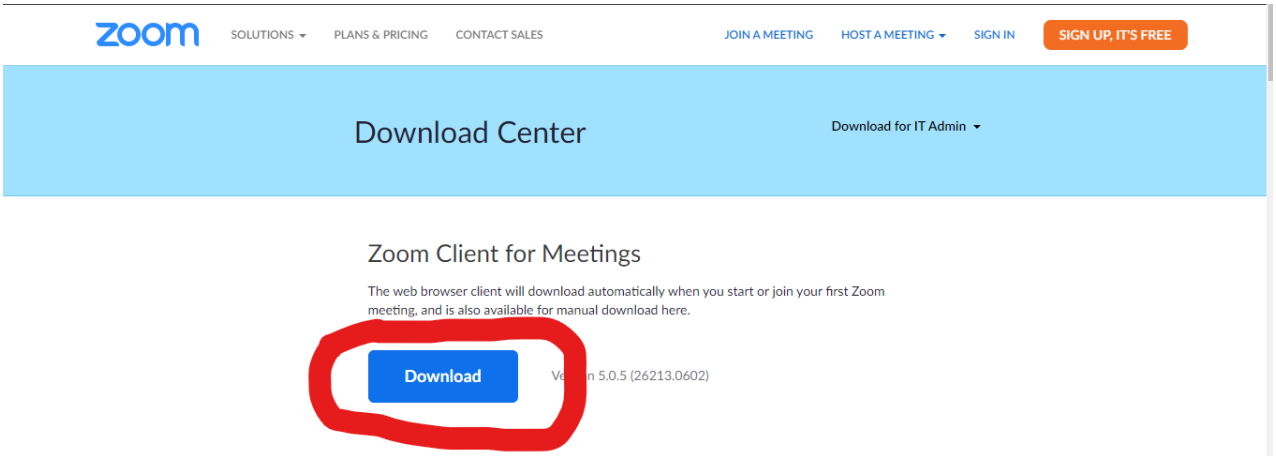
4. Enter your computer administrator's username and password.

5. Change ‘Allow apps downloaded from:’ to ‘App Store and identified developers’.

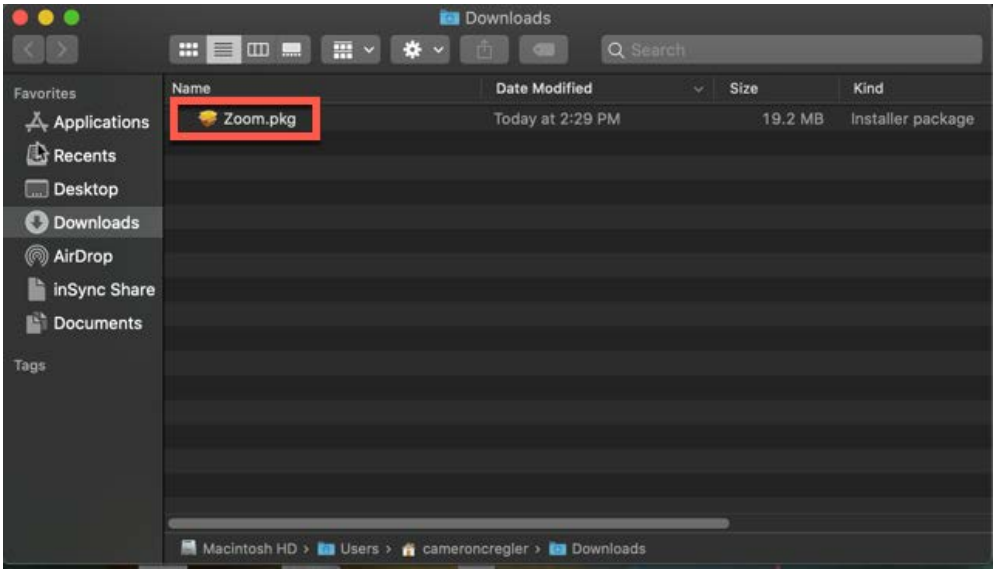


Note: For Mac High Sierra (10.13.x), you will need to click on ‘Allow’ too.

6. Open up Safari, type and go to https://zoom.us/download. Click 'Download' under 'Zoom Client for Meetings'.

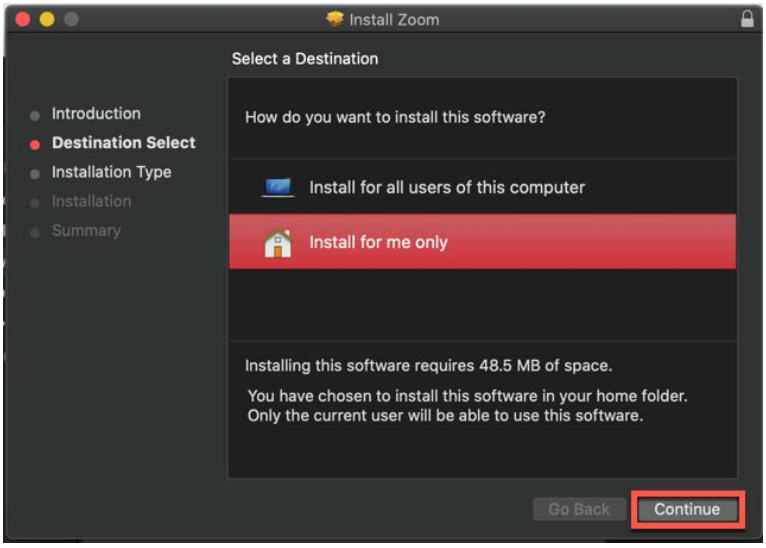


7. Open 'Finder'. Open the Downloads folder. Open the Zoom.pkg file.

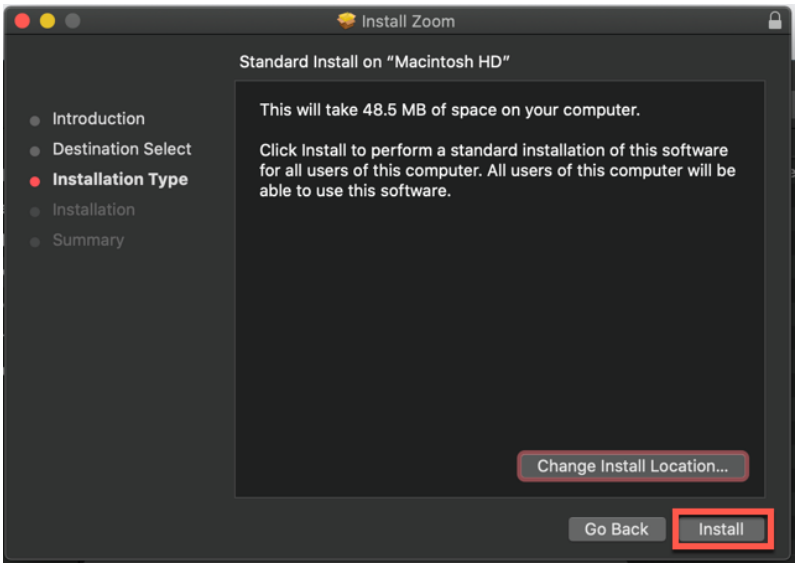


8. Once the installer opens, click ‘Continue’.

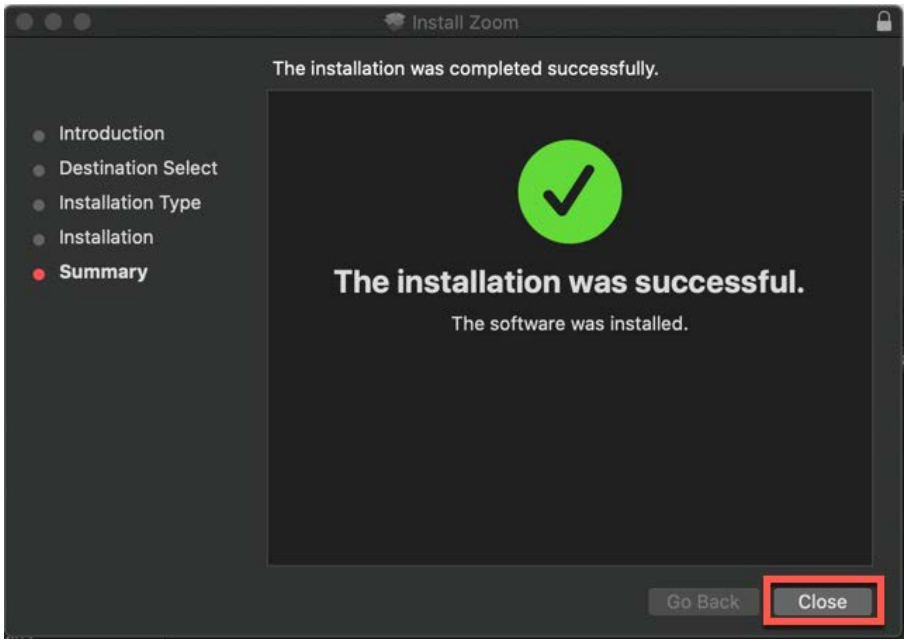
9. Click ‘Install only for me’. Click ‘Continue’.



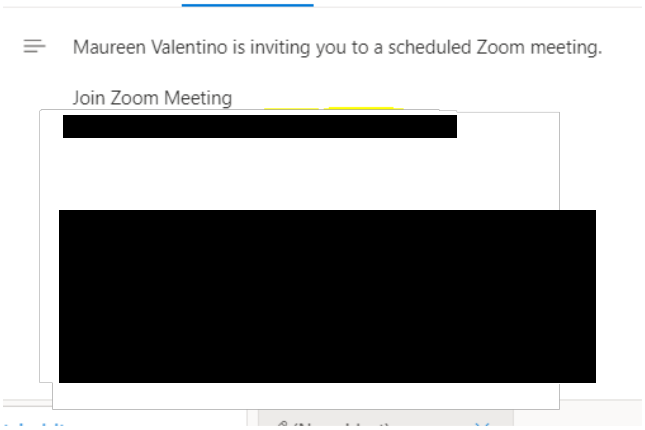
10. Click ‘Install’.



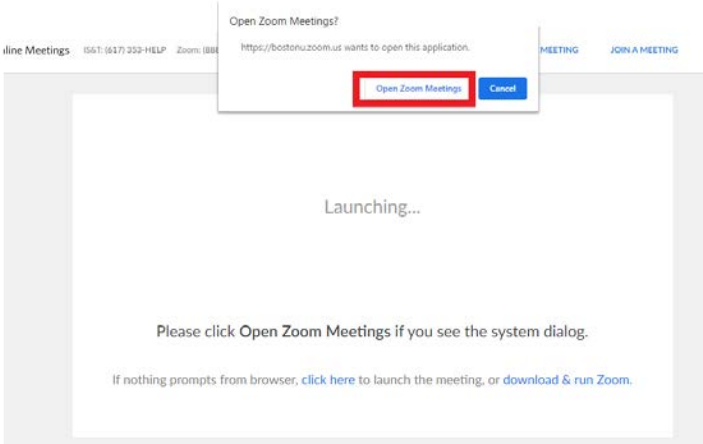
11. Once the installation is complete, click ‘Close.’



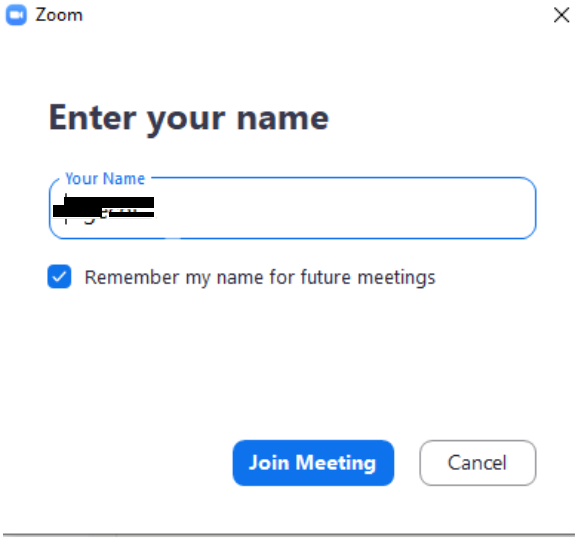
12. Head back to the email with the Zoom invite and click the link under ‘Join Zoom Meeting’.



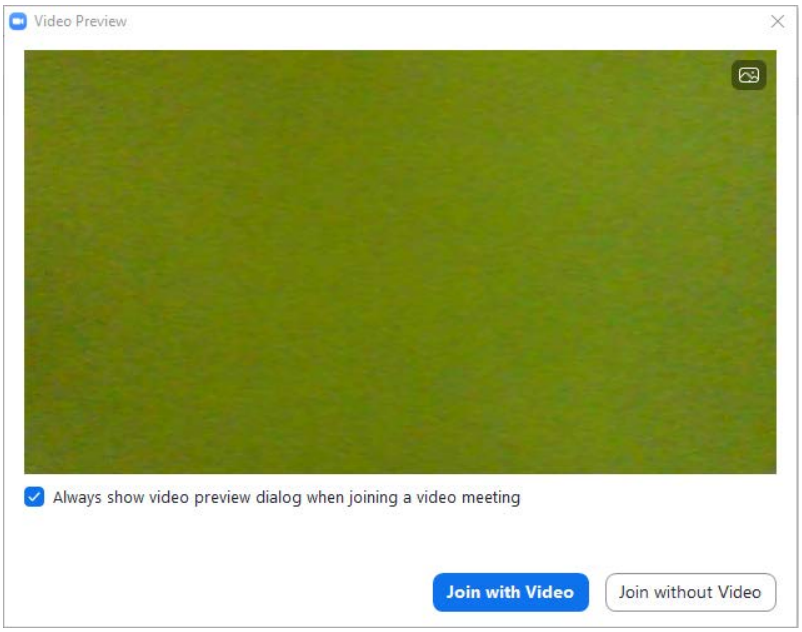
13. A popup should appear, click ‘Open’ or ‘Open Zoom Meeting’.



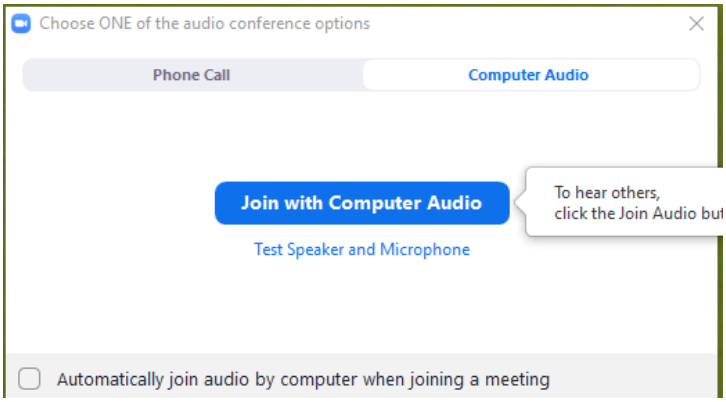
14. The Zoom application should open up. Type your name and click ‘Join Meeting’.



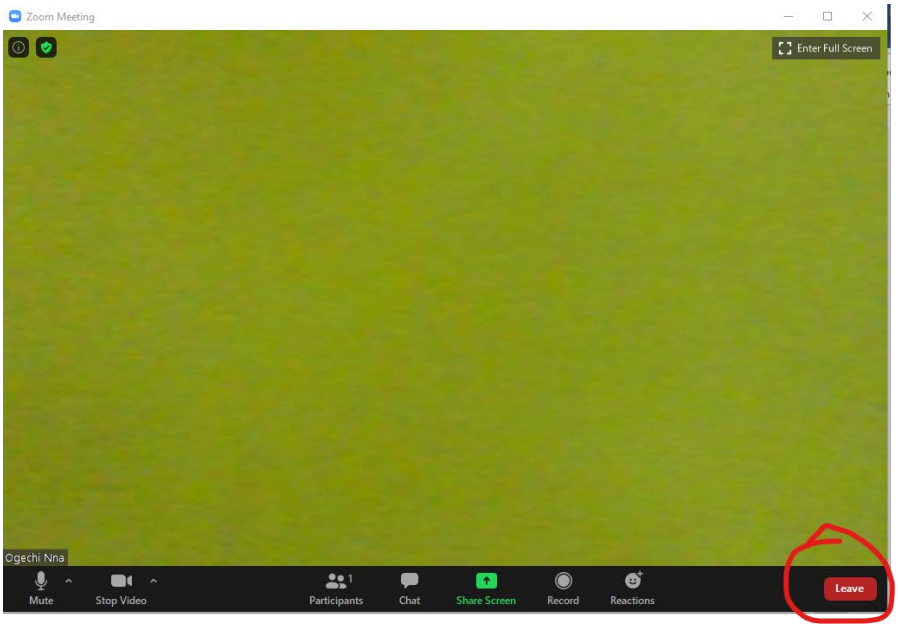
15. A preview video should appear, click ‘Join with Video’.



16. You should now be connected to the Zoom meeting, click ‘Join with Computer Audio’ to access the audio in the Zoom Meeting.



17. To leave the Zoom meeting, click ‘Leave Meeting’ located on the bottom right bar.

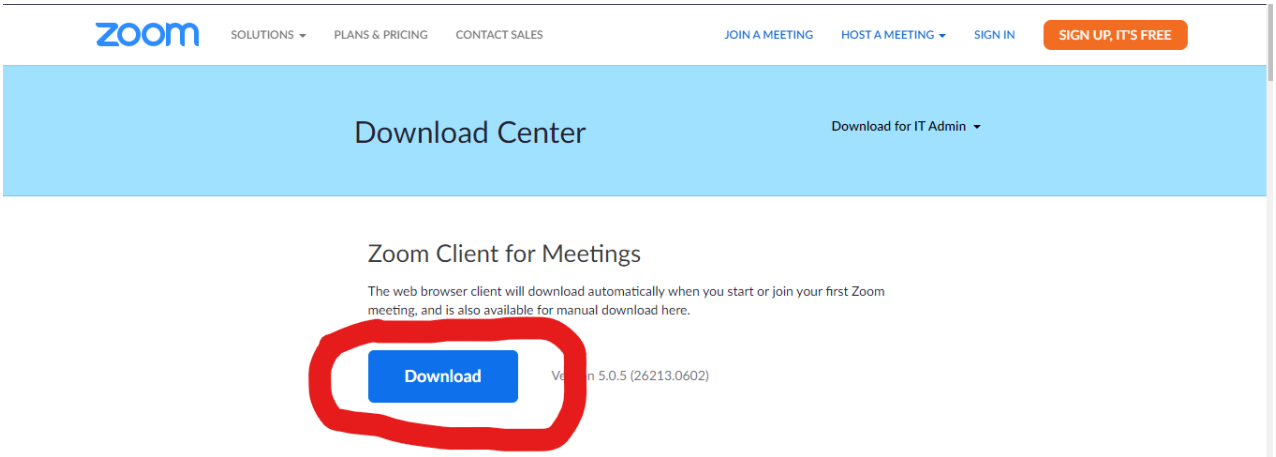


Source: https://support.zoom.us/hc/en-us/articles/203020795-How-To-Install-on-Mac

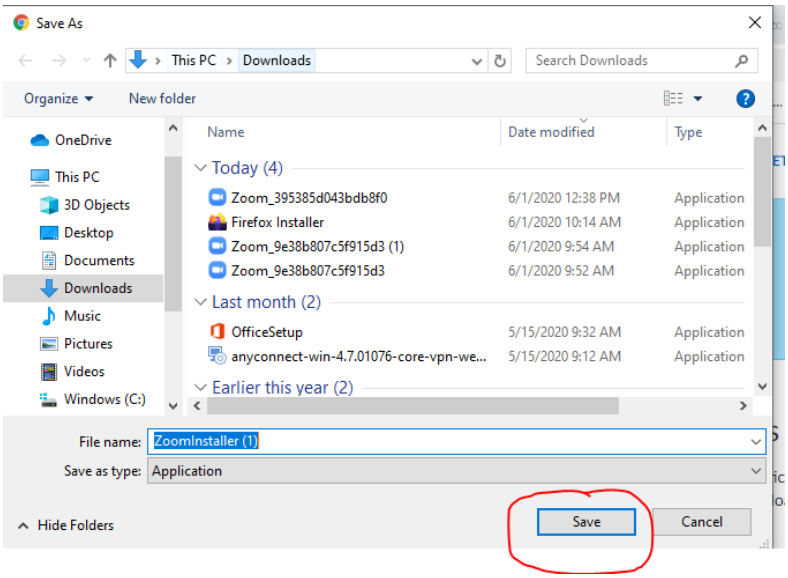
Appendix E: Zoom Instructions for Windows

DOWNLOADING ZOOM FOR WINDOWS AND ACCESSING ZOOM MEETING

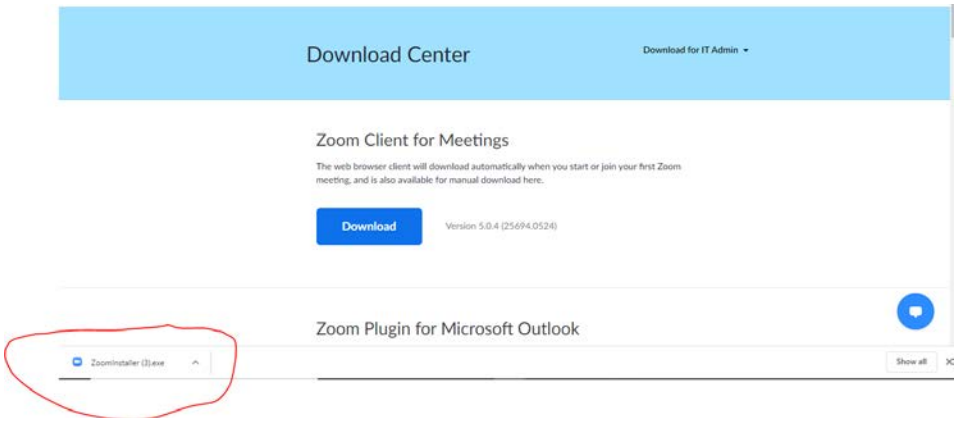
1. Go to to https://zoom.us/download. Click 'Download' under 'Zoom Client for Meetings'.



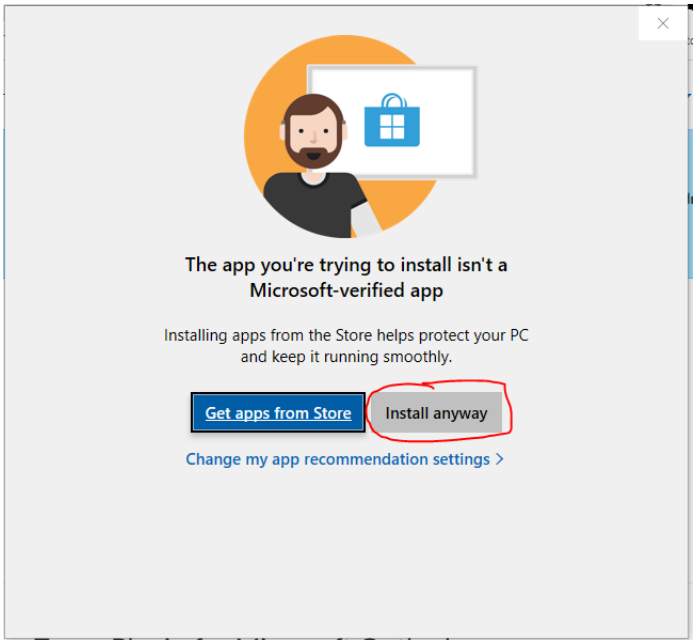
2. A popup should appear. Click 'Save' on the ZoomInstaller file.



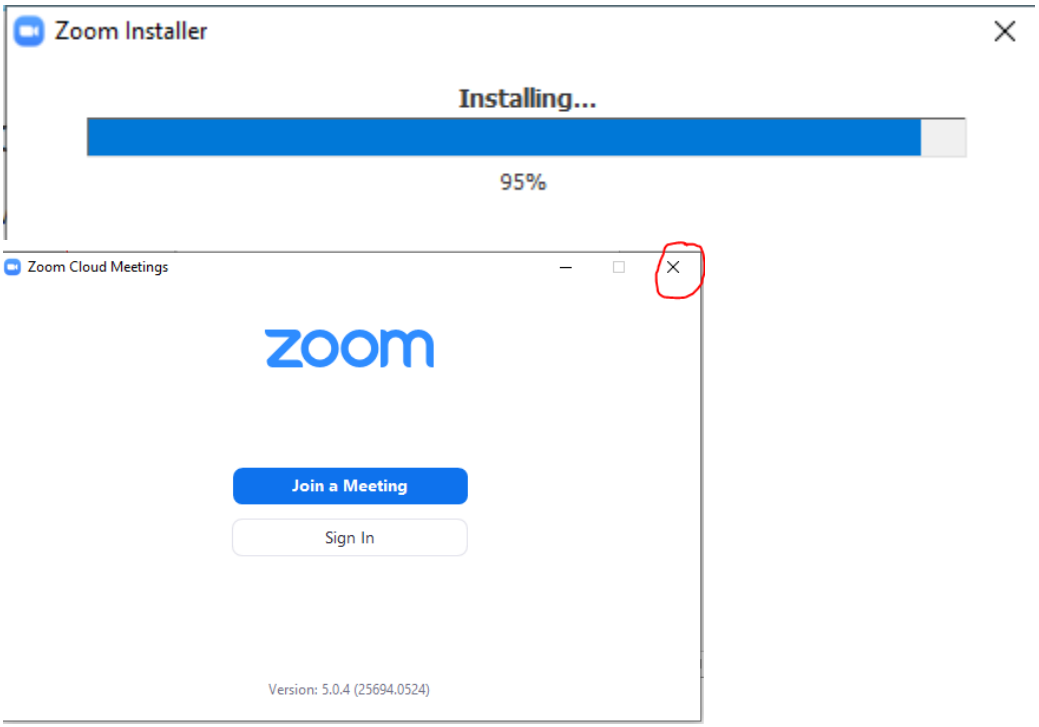
3. A download bar should appear at the bottom. Once finished downloading click on the application.



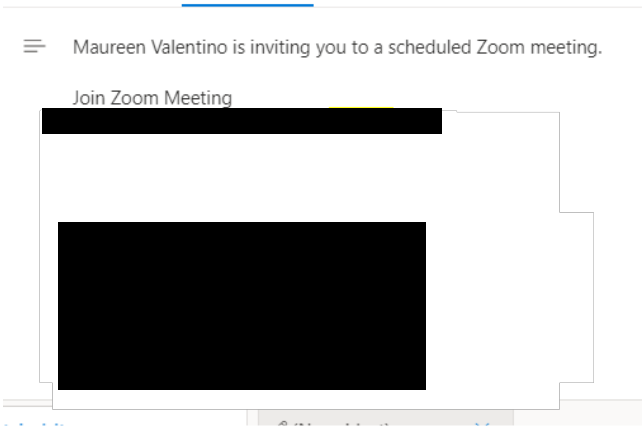
4. ****If you have Windows 10 a popup may appear as shown below regarding apps (depending on settings). Click 'Install anyway' if this happens.****



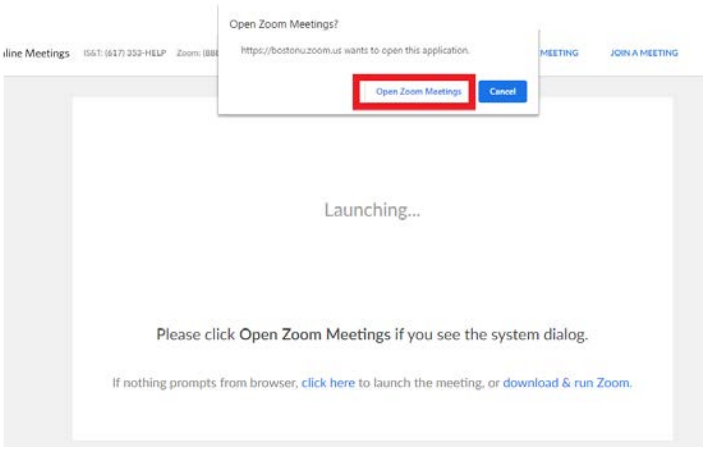
5. An installation bar will appear. Once installed you'll be prompted to 'Sign in' or 'Join a Meeting'. **You do not have to sign in, just exit out.**



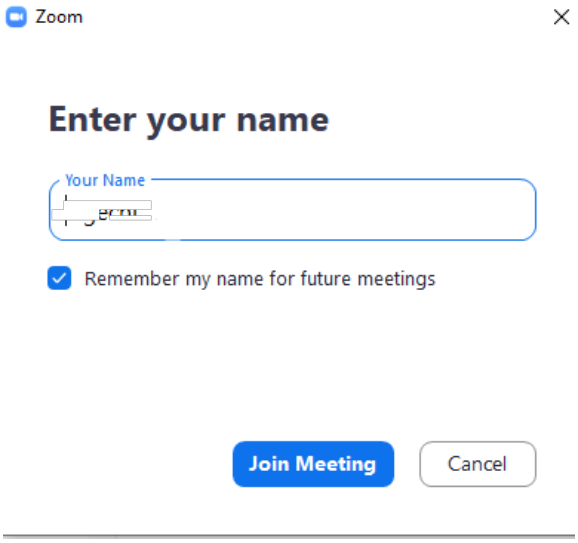
6. Head back to the email with the Zoom invite and click the link under 'Join Zoom Meeting'.



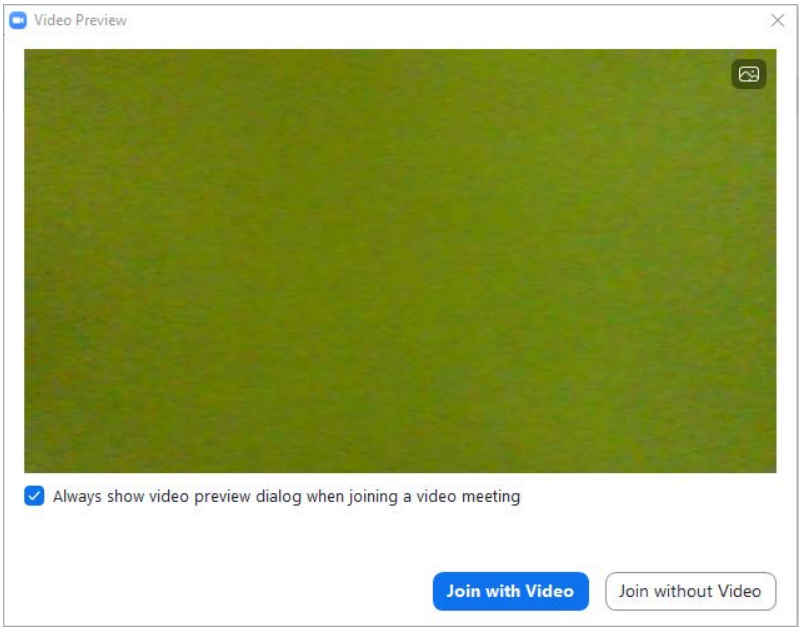
7. A popup should appear, click ‘Open’ or ‘Open Zoom Meeting’.



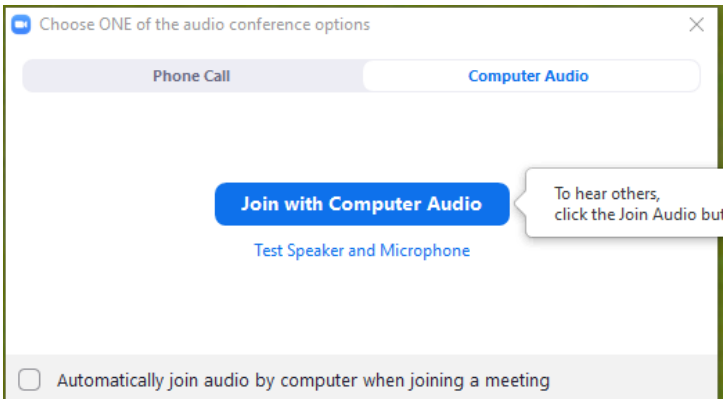
8. The Zoom application should open up. Type your name and click ‘Join Meeting’.



9. A preview video should appear, click ‘Join with Video’.



10. You should now be connected to the Zoom meeting, click ‘Join with Computer Audio’ to access the audio in the Zoom Meeting.



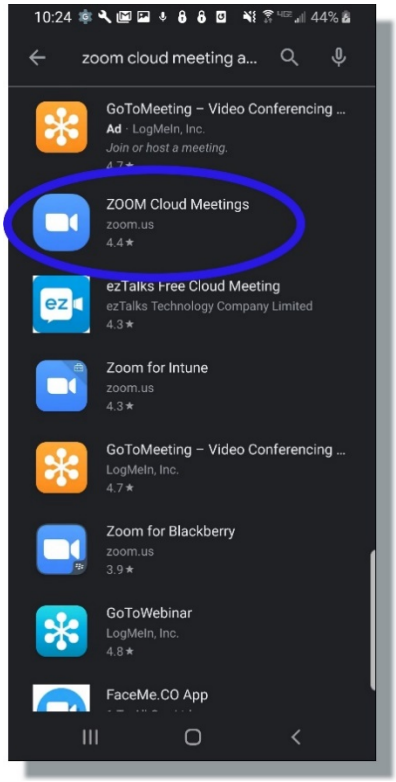
11. To leave the Zoom meeting, click ‘Leave Meeting’ located on the bottom right bar.

Appendix F: Zoom Instructions for Android

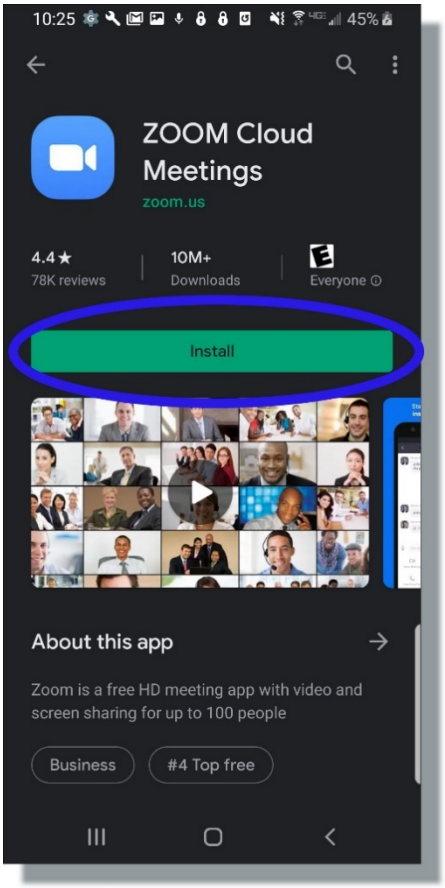
ZOOM INSTRUCTIONS FOR ANDROID

1. Tap on the Google **Play Store** icon.

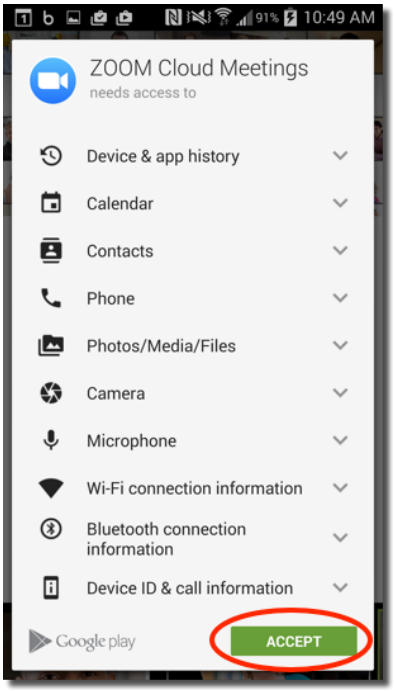
2. In Google Play, tap on Apps. Enter zoom in the search text area, and then tap 'ZOOM Cloud Meetings' from the search results.



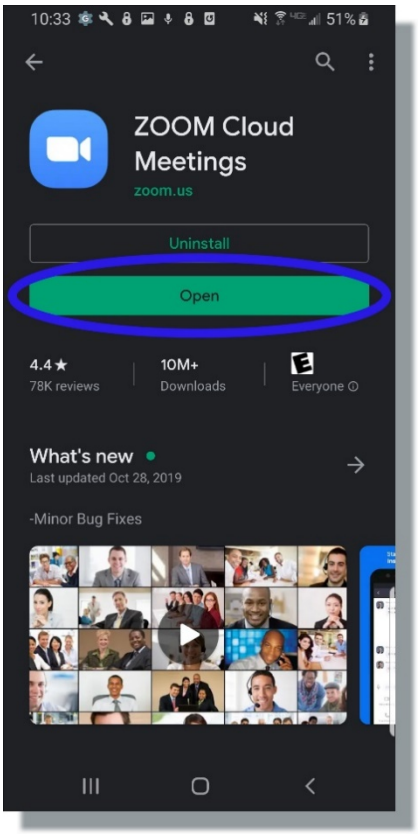
3. In the next screen, tap ‘Install’.



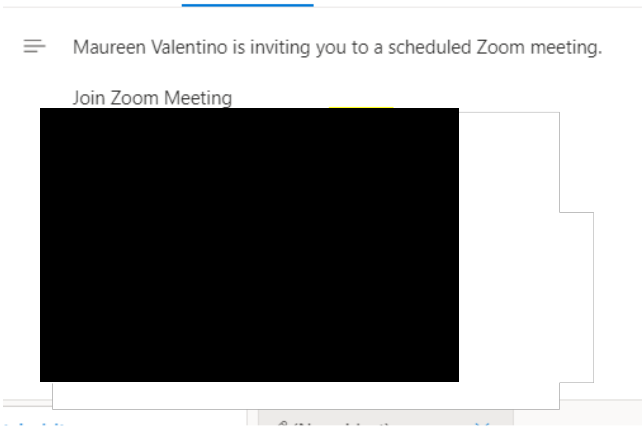
4. In the next screen, tap ‘Accept’.



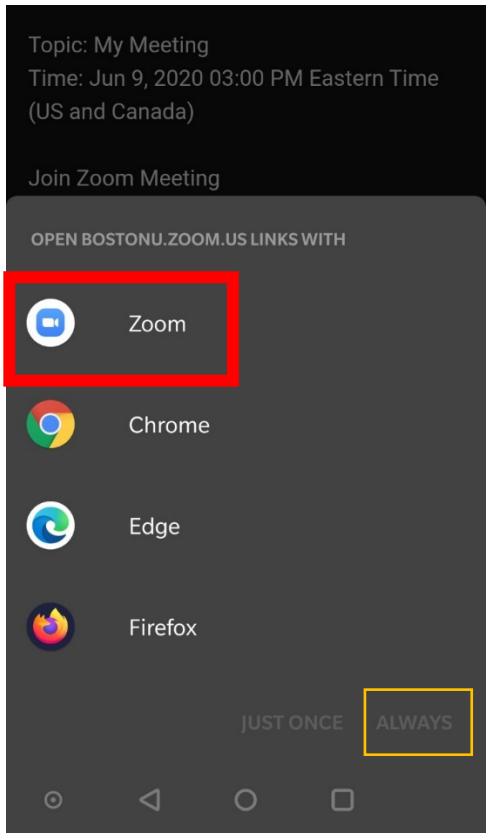
5. After Zoom has installed, tap ‘Open’.



6. Go back to the Zoom invite email and tap the link under ‘Join Zoom Meeting’.



7. A popup should appear with a list of browsers and applications. Tap on the ‘Zoom’ application. Select ‘Always’ on the bottom bar.

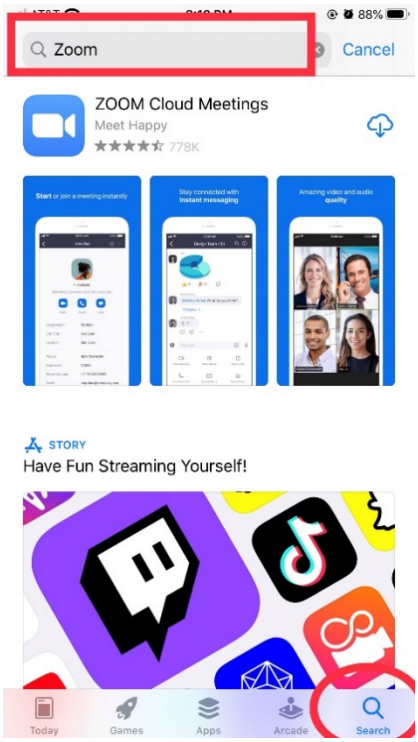


8. The Zoom app should open back up connecting you to the Zoom meeting. Make sure you tap ‘Accept’ for access to your device’s **audio and video.**

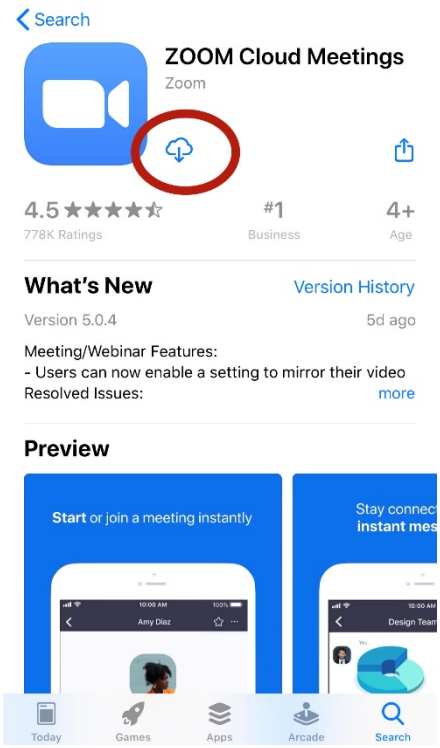
Appendix G: Zoom Instructions for iOS (iPAD)

DOWNLOADING ZOOM ON iOS (iPAD)

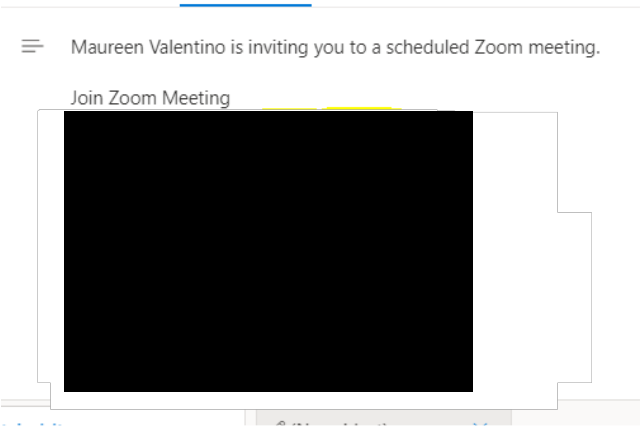
1. Go to the ‘App Store’ and search ‘Zoom’. Tap on ‘Zoom Cloud Meetings’.



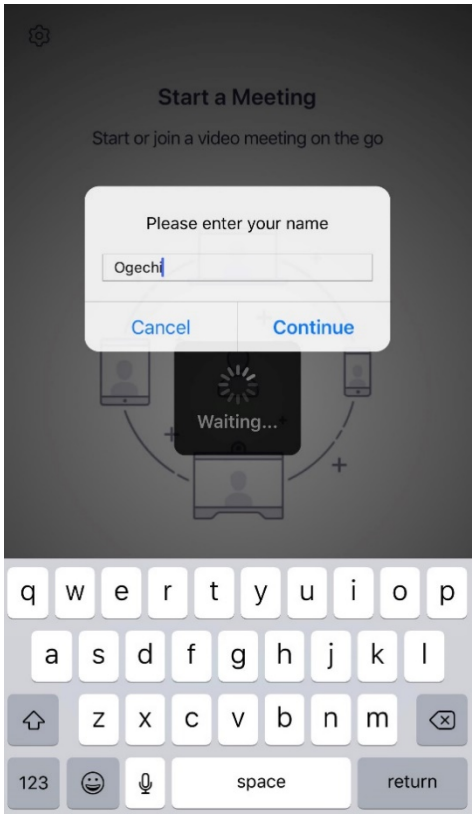
2. Download the app by tapping on the cloud.
   Note: You may need to enter your Apple ID passcode**



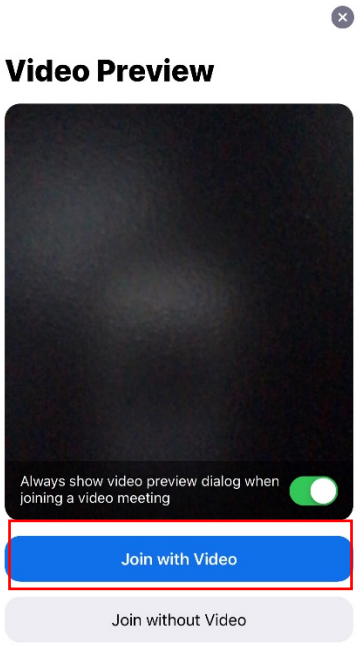
3. Once downloaded, head back to the email containing the Zoom invite. Tap the link under 'Join Zoom Meeting'.

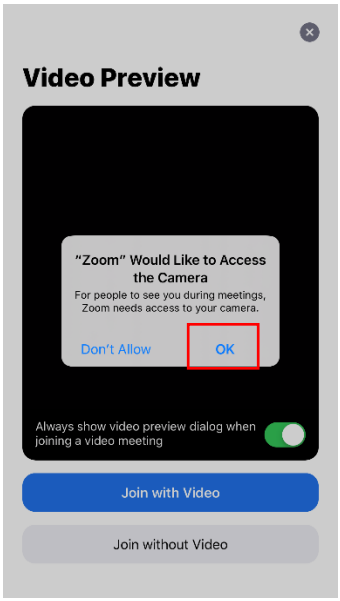


4. The meeting should open in the app. You will be prompted to type in your name. Tap ‘Continue’.

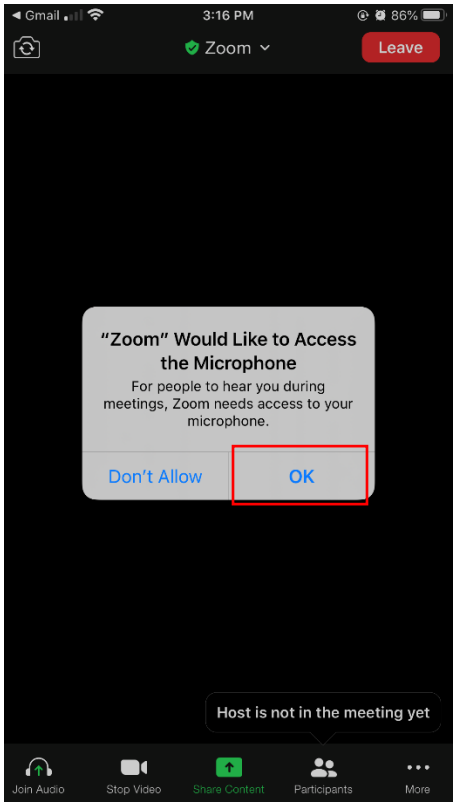


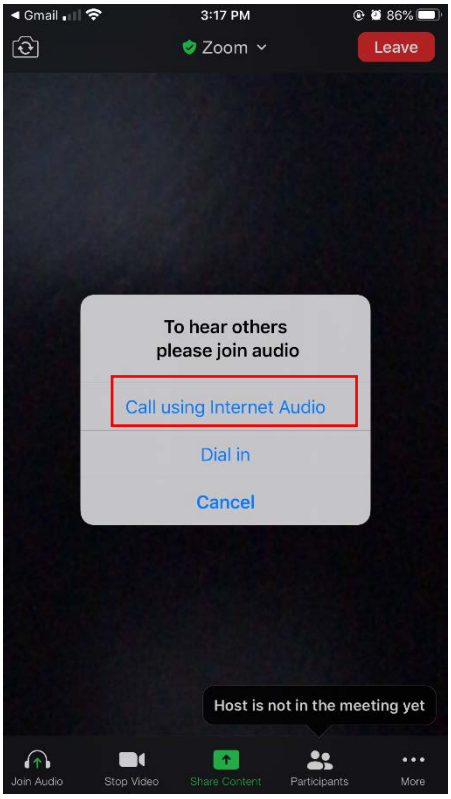
5. The next screen should display a video preview, tap ‘Join with Video’. Allow Zoom to Access Camera by tapping ‘Ok’.





6. Allow Zoom to Access the Microphone by tapping ‘Ok’. Next, tap ‘Call using Internet Audio’ to connect to Zoom audio.

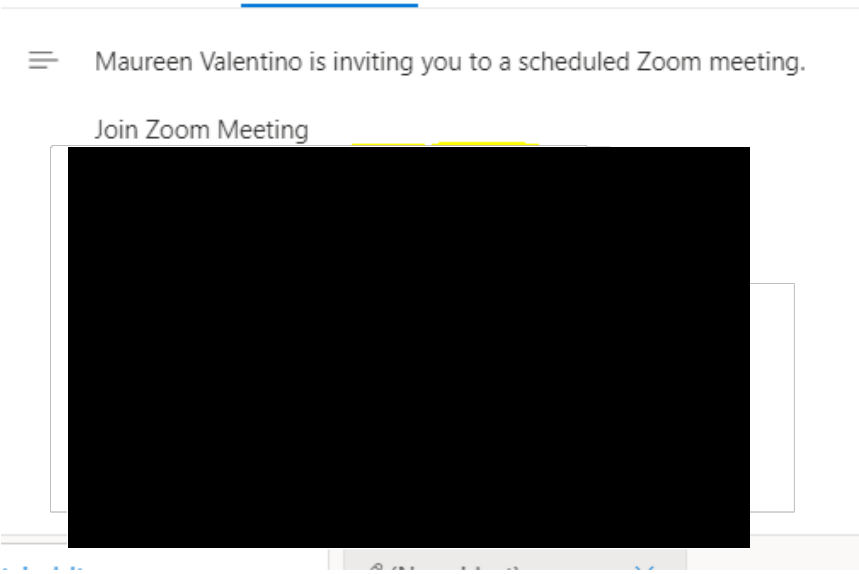




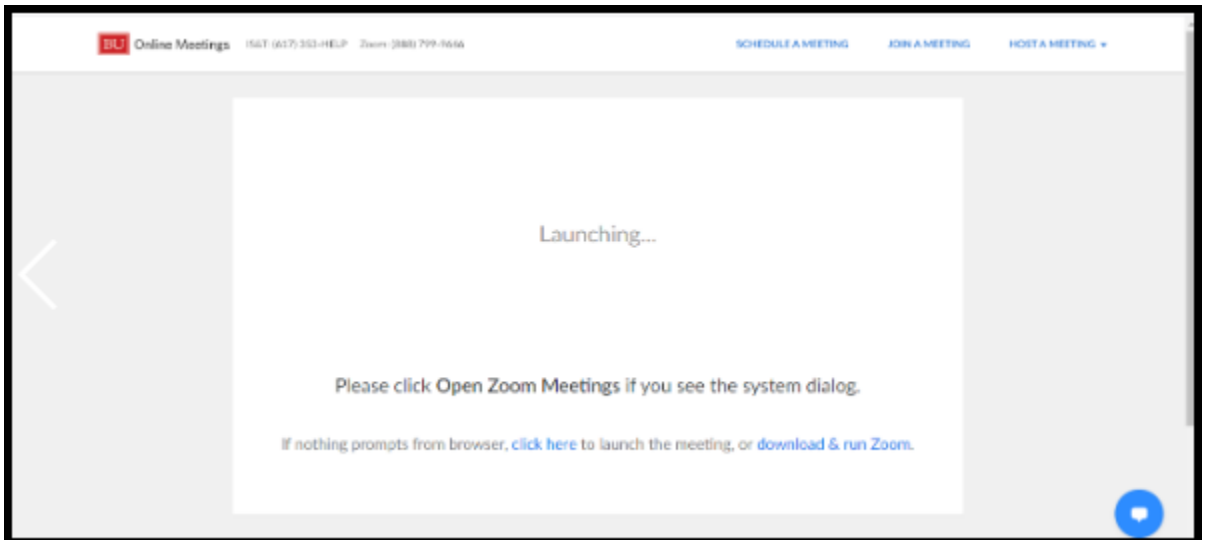
Appendix H: Instructions for Joining Meeting

ZOOM INSTRUCTIONS

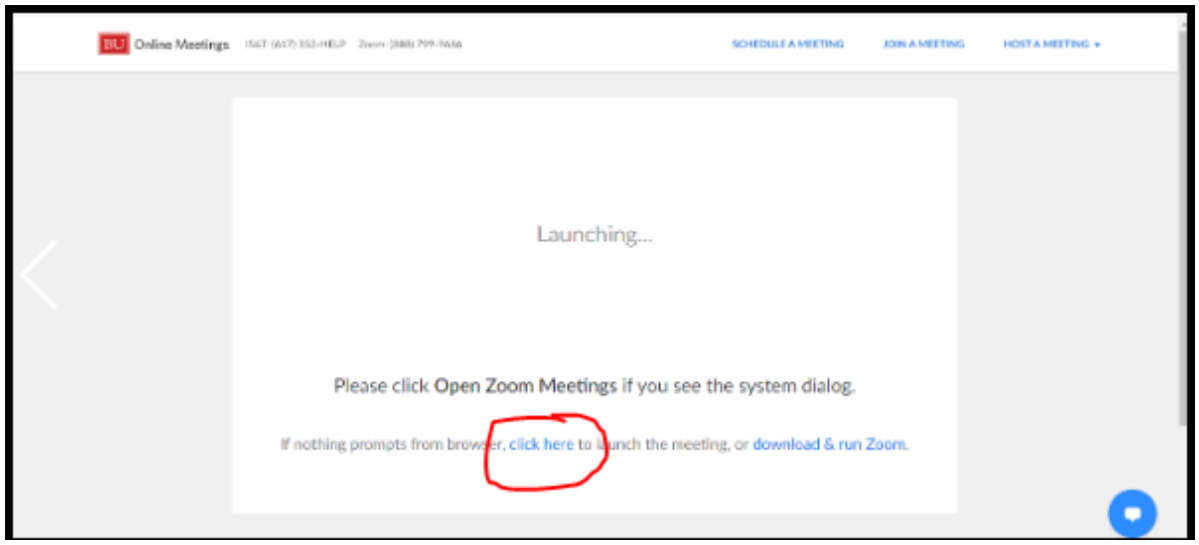
1. Go to the Zoom invite email and click the link under 'Join Zoom Meeting'.



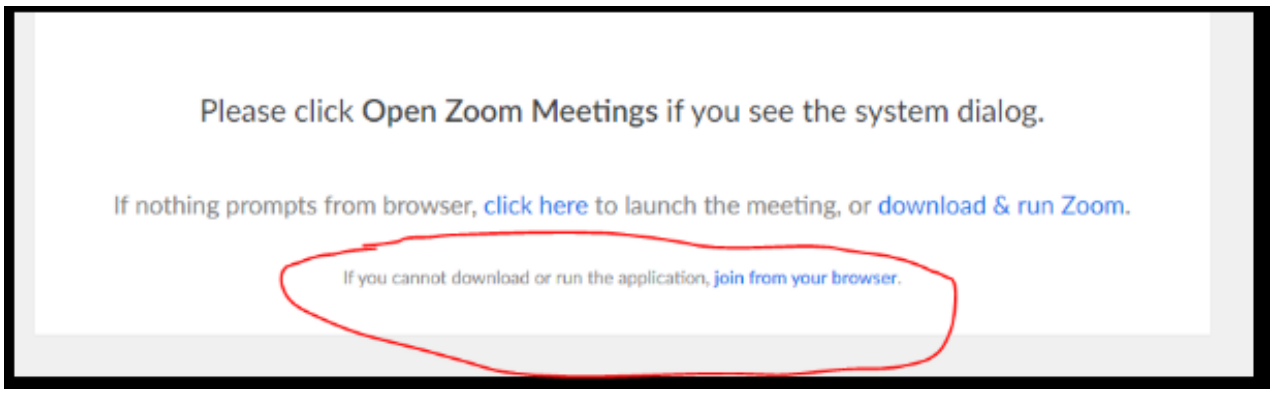
2. It will open up a new browser, **please wait a few seconds until your page looks like this:**



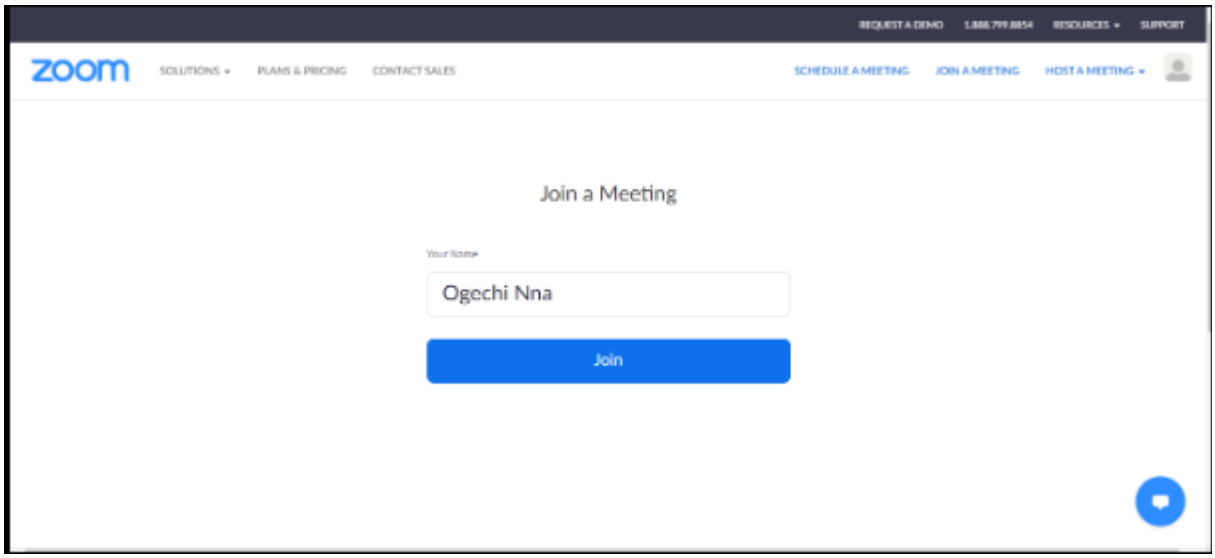
3. Click on ‘Click here’.



4. Once you click the link, it should open up a prompt on the same page: ‘If you cannot download or run the application, join from your browser.’ Click on the hyperlink ‘join from your browser’.



5. A new page will load to type in your name. Type your name in and click the blue ‘Join’ tab.



6. You will be prompted to the Zoom meeting. Click the blue ‘Join Audio by Computer’ to connect to the audio of the Zoom meeting.

   - Click the ‘Start Video’ button on the bottom left to connect to the webcam.
   - Click ‘Leave Meeting’ on the bottom right once the meeting has ended to exit the meeting.