Manual 21

Atherosclerosis Risk in Communities - Cognitive Impairment and Dementia, Vascular Brain Injury, and Atrial Myopathy: Implications for Prevention of Alzheimer's Disease-Related Dementias

ARIC-AMP

Zio® XT Monitor Procedures

January 5th, 2024 - Version 1.1

Study website - http://www.cscc.unc.edu/aric/

Table of Contents

1. Introduction

Dear Atherosclerosis Risk in Communities Study investigators and staff:

The Atherosclerosis Risk in Communities Study Cognitive Impairment and Dementia, Vascular Brain Injury, and Atrial Myopathy: Implications for Prevention of Alzheimer's Disease-Related Dementias (ARIC-AMP) team is delighted to present you with this manual of procedures (MOP). ARIC-AMP is an extension of ARIC that you helped make so successful. This MOP will provide you with the information necessary to recruit participants and successfully apply the Zio® XT Monitor, a small, lightweight device used clinically to detect cardiovascular issues. The MOP will also describe how to follow up with participants, answer their questions, and provide medical results.

The ARIC-AMP Principal Investigators are Drs. Lin Yee Chen, Amil Shah, and Thomas Mosley. Please feel free to contact us using the information in Appendix 1 should you have any questions or suggestions to help make our study successful.

Sincerely,

Lin Yee Chen, MD, MS
Director, Lillehei Heart Institute
Fred C. and Katherine B. Andersen Foundation Chair in Adult Cardiology
Professor of Medicine
University of Minnesota Medical School
420 Delaware Street SE, MMC 508 Mayo
Minneapolis, MN 55455

Amil M. Shah, MD, MPH
Dallas Heart Ball Chair in Cardiac Research
Department of Internal Medicine,
UT Southwestern Medical Center
Dallas, Texas 75390

Thomas H Mosley, PhD
Director MIND Center University of Mississippi Medical Center
Robbie and Dudley Hughes Distinguished MIND Center Chair
Professor School of Medicine, Department of Neurology
University of Mississippi Medical Center
Jackson, MS 39216

2. Abbreviations

AD	Alzheimer's Disease
ADRD	Alzheimer's Disease and Related Dementias
AF	Atrial Fibrillation
AM	Atrial Myopathy
AMP	Atrial Myopathy Progression
APOE-ε4	**ε4** allele of the Apolipoprotein E gene
ARIC	Atherosclerosis Risk in Communities Study
ARIC-AMP	Atherosclerosis Risk in Communities Study - Cognitive Impairment and Dementia, Vascular Brain Injury, and Atrial Myopathy: Implications for Prevention of Alzheimer's Disease-Related Dementias
CC	Coordinating Center
CDART	Carolina Data Acquisition and Reporting Tool
CNS	Central Nervous System
CVD	Cardiovascular Disease
ECG	Electrocardiogram
FC	Field Center
GFAP	Glial Fibrillary Acidic Protein
IRB	Institutional Review Board
LA	Left Atrial
LC	Lead Center
MCI	Mild Cognitive Impairment
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
NfL	Neurofilament Light
NIH	National Institutes of Health
OSMB	Observational Study Monitoring Board
PAC	Premature Atrial Contraction
PI	Principal Investigator
PVC	Premature Ventricular Contraction
sIRB	Single Institutional Review Board
SVE	Supraventricular Ectopy
VCID	Vascular Contributions to Cognitive Impairment and Dementia
VE	Ventricular Ectopy
VRF	Vascular Risk Factors

3. Overview

Alzheimer's Disease (AD) and AD-Related Dementias (ADRD) are projected to affect 115 million people worldwide by 2050. Vascular contributions to cognitive impairment and dementia (VCID)-a primary type of ADRD-is a major research focus for the NIH, which has called for the need to discover novel non-invasive, non-CNS organ-related (e.g., heart) markers to detect the presence and progression of VCID (ADRD summit 2022). The oldest-old (>85 years) are the fastest growing segment of the population in most of the world and have the highest rates of dementia. Yet, the risk factors for AD/ADRD in the oldest-old are poorly understood and are different from the young-old (65-74 years) and middle-old (75-84 years). For example, in the oldest-old, hypertension is protective, and about half of all dementia cases in the oldest-old is related to non-AD pathologies such as microbleeds and small vessel ischemic disease. Our team and others have shown robust associations of midlife modifiable vascular risk factors (VRF) with cognitive decline, mild cognitive impairment (MCI), dementia, and imaging markers of dementia. However, as VRF and APOE-ε4 no longer predict cognitive impairment in studies of the oldest-old, more research is urgently needed.

Atrial myopathy (defined by altered left atrial [LA] function or structure) is an underrecognized but important contributor to VCID, and is associated with lower cognitive function, greater vascular brain injury, and incident dementia. Our data from the Atherosclerosis Risk in Communities (ARIC) study demonstrate a 33% higher risk of developing dementia (95% CI, 18–51%) over 6-year follow-up associated with a 1-SD (7.7%) decrement in LA reservoir strain (a measure of LA function) among older adults (mean age, 75 years), independent of cardiovascular disease (CVD) and dementia risk factors including atrial fibrillation (AF) and APOE-ε4. Atrial myopathy was also associated with greater global cortical β-amyloid (AD pathology). However, the extent to which atrial myopathy is associated with dementia risk in the oldest-old is unknown. Furthermore, prior research has evaluated atrial myopathy as a static entity and the etiology and prognostic relevance of atrial myopathy progression are not known. These are crucial barriers to targeting this potentially modifiable risk factor for AD/ADRD prevention. Thus, our overarching objectives are to determine the prognostic importance of atrial myopathy for incident dementia in the oldest-old; relate atrial myopathy progression or trajectories of atrial myopathy in the young-old and middle-old to incident dementia and change in neuroimaging and plasma biomarkers of AD/ADRD; and define the clinical/lifestyle risk factors and proteomic and metabolomic signatures of adverse atrial myopathy trajectories. We will extend and amplify our findings from LA function at ARIC Visit 5 (V5; age range, 71-90 years) by funding measurement of LA function on existing and funded serial echocardiograms at Visit 7 (V7) (age range, 77-97 years) and V11 (age range, 81-101 years) to identify trajectories of atrial myopathy progression from young-old to oldest-old.

We will recruit ~1,700 V11 participants to wear the Zio® XT Monitor created by iRhythm Technologies, Inc. for 14 days of consecutive monitoring of cardiac rhythm activity. This will allow us to determine the extent to which AF contributes to any associations with cognitive, imaging, or biomarker outcomes.

- **Aim 1:** Evaluate the association of longitudinal change in LA function and LA function trajectories with neurocognitive outcomes in the oldest-old.
- **Aim 2:** Relate longitudinal change in LA function to neuroimaging and plasma biomarkers of AD/ADRD neuropathology.
- **Aim 3:** Identify lifestyle and molecular risk factors for longitudinal change in LA function and LA function trajectories.

4. Training and Certification

All ARIC Field Center (FC) Staff involved in the Zio® XT Monitor protocol will participate in a web-based training. This training will cover application of the Zio® XT Monitor and procedures for reporting results to the participants. COVID-19 safety procedures documented in Appendix 2 will also be reviewed.

Dr. Chen and representatives from iRhythm will conduct one training session with all sites via Zoom. The training will be recorded for those unable to attend and for future reference. Refresher trainings will be provided by Dr. Chen's staff on an as needed basis. Instructions for the FCs to register with the Zio® XT Monitor portal (https://www.ziosuite.com/) will be provided before the training. The project manager at iRhythm will set up Zio® XT Monitor portal accounts for FC staff who either attend the Zoom training or complete it subsequently. Appendix 3 includes information on portal enrollment.

After the staff member completes the web-based training, they will be required to conduct at least 2 successful practice rounds of the Zio® XT Monitor in-person protocol under the supervision of a trained senior FC staff member. They may also complete 2 successful practice rounds of the phone-based protocol, again under the supervision of a trained senior FC staff member. Descriptions of the steps involved in each practice round are detailed below. Checklists are provided in Appendix 4. Once the protocol has been appropriately conducted, the senior FC staff member will send an email to arichelp@unc.edu. The email will include the name and staff ID of the individual certified.

4.1 Certification for In-Person Protocol

The in-person protocol is comprised of the following key components:

1. Clearly and accurately explaining the protocol including length of wear, what to do about bathing/showering, whom to contact with questions, etc.
2. Labeling Zio® XT Monitor kit with the correct participant ID and monitor serial number as well as documenting the monitor serial number within Carolina Data Acquisition and Reporting Tool (CDART). Labeling participant mailer with Field Center specific ID.
3. Logging into the ZioSuite portal.
4. Simulating registering Zio® XT Monitor in ZioSuite, linking to participant ID.
5. Demonstrating the proper technique for site preparation including washing hands and wearing gloves, cleaning the area of debris, identifying the correct placement site, removing clothing covering placement site, shaving of skin, and preparing skin using abrader pad.
6. Demonstrating the proper technique for monitor placement including affixing and activating the device, providing individual with instructions if they experience discomfort, correctly answering all questions asked, cleaning the area of debris, and disposing of any potentially biohazardous waste appropriately.

Please note that during these practice rounds monitors do not need to be worn for 14 days—just placed. In addition, practice rounds can be conducted with FC staff acting as the participant.

Once a staff member has completed the online training and successfully placed at least 2 Zio® XT Monitors, the staff member is considered certified to perform the in-person protocol with ARIC participants even if they have not yet been certified on the phone-based protocol.

4.2 Certification for Phone-Based Protocol

The phone-based protocol is comprised of the following key components:

1. Labeling Zio® XT Monitor kit with the correct participant ID and monitor serial number as well as documenting the monitor serial number within CDART prior to shipment. Labeling participant mailer with Field Center specific ID.
2. Logging into the ZioSuite portal.
3. Simulating registering Zio® XT Monitor in ZioSuite, linking to participant ID.
4. Clearly and accurately explaining the protocol over the phone including length of wear, what to do about bathing/showering, whom to contact with questions, etc.
5. Explaining the proper technique for site preparation over the phone including washing hands, identifying the correct placement site, removing clothing covering placement site, cleaning the area of debris, shaving of skin, and preparing skin using abrader pad.
6. Explaining the proper technique for monitor placement over the phone including affixing the device, providing individual with instructions if they experience discomfort, and correctly answering all questions asked.
7. Instructing the participant over the phone to turn on the device and ensure correct response.

During these practice rounds, the FC staff member being certified and the individual who is wearing the device ***should not be in the same room***. Also, monitors do not need to be worn for 14 days—just successfully placed. In addition, practice rounds can be conducted with FC staff acting as the individual who is wearing the device.

Once a staff member has completed the online training and successfully guided at least 2 individuals through placement of the Zio® XT Monitor over the phone, they will be considered certified to perform the phone-based protocol with ARIC participants even if they have not yet been certified on the in-person protocol.

5. Site Qualification

All sites must obtain Institutional Review Board (IRB) approval for ARIC-AMP and have at least one staff member certified in the in-person ***or*** one staff member certified in the phone-based protocol before contacting participants.

6. Recruitment

6.1 Introduction

ARIC participants who have an echocardiogramconsent to participation in ancillary studies at V11 will be eligible to enroll in ARIC-AMP. Participants who are initially eligible can be identified via CDART. FCs may contact participants to begin the screening and recruitment process by mail utilizing invitation letters, by email utilizing invitation emails, by phone using recruitment scripts, or during a clinic visit using recruitment scripts. These materials are available at https://sites.cscc.unc.edu/aric/Ziopatch.

If a participant has diminished capacity, it may be necessary to contact a ***proxy*** who can speak on behalf of the participant. Invitation letters and scripts have been prepared for these

situations. For additional information about when it may be necessary to contact a proxy, please refer to ARIC Manual 2.

If a proxy is required and the Zio® XT Monitor is to be applied remotely, the proxy must be available to assist the participant with application. Any materials or reports sent through the mail should be addressed to the proxy.

6.2 Eligibility

Before consenting the participant, eligibility must be determined and documented in CDART using the Screening and Eligibility form ***(Form Code: EIO)***. The eligibility interview may be conducted over the phone during the initial recruitment call, during a later call, or in-person during a clinic visit.

During the screening, participants who meet one or more of the following criteria will be excluded:

- History of allergic skin reaction to adhesive tape
- Implantable cardiac device such as a pacemaker.
- Implanted neurostimulator.

Participants who plan to travel by plane or complete a medical scan such as an X-ray in the next 14 days will not be excluded but will be invited to enroll after these events have transpired.

6.3 Consent and Enrollment

The enrollment status of each participant who is invited to take part in ARIC-AMP must be documented in the ARIC-AMP Screening and Consent Form (***Form Code: EIO***).

If the participant plans to come to the clinic to enroll in ARIC-AMP, then an information packet that contains the following should be provided in advance:

- Appointment date and time
- Directions to the clinic (e.g., a map) and parking facilities
- Consent form *without signature pages*
- Verbal Consent Handout
- Frequently Asked Questions
- Transportation, if applicable

For participants enrolling in person, FC staff will obtain written consent utilizing the forms at https://sites.cscc.unc.edu/aric/Ziopatch. After describing the study and ensuring understanding of the commitment, risks, and benefits, individuals who agree to participate must sign and date the Consent form.

When a proxy is required, ARIC-AMP requires signatures on the Consent form from both the proxy and the participant.

If the participant plans to enroll in ARIC-AMP remotely and receive the Zio® XT Monitor kit in the mail, staff will utilize the forms and scripts at https://sites.cscc.unc.edu/aric/Ziopatch to obtain and document verbal consent. A copy of the Consent form without signature pages and the Verbal Consent Handout will be included with the materials sent by mail.

When a proxy is required, ARIC-AMP requires verbal consent from both the proxy and the participant.

In addition to giving consent to participate in the study, participants or their proxies will be asked whether they give consent to receive results from the device, either by mail or email. The participant or proxy may agree to one method, both, or neither. When consenting participants, FC staff should remind them that if they do not agree to either method, then they will not receive results. The preference of the participant will be documented in the consent form

6.4 Quality Assurance for Recruitment

On a monthly basis, the CC will generate detailed tabulations to ensure recruitment objectives are being met and that the participants enrolled reflect the target population. Reports created by the CC will be reviewed by the ARIC-AMP project manager, PIs, and lead statistician. Feedback will be provided during regular conference calls with FC study coordinators for problem-solving and improving procedures when possible.

7. Assessment

After consent is obtained, the participant will be asked to wear the Zio® XT Monitor for 14 days. The device may be removed at any time on the 14th day but preferably towards the end of the day. Prior to application or mailing the kit to a participant, the monitor must be registered in the iRhythm portal (https://www.ziosuite.com).

Everything needed to apply the Zio® XT Monitor is included in the Zio® XT Monitor kit, except for an additional pre-paid mailer that will need to be provided to the participant so they can return the monitor to the field center. The Zio® XT Monitor should not be placed on broken, damaged, or irritated skin. The Zio® XT Monitor should be removed prior to X-ray, computed tomography, or MRI scans. The Zio® XT Monitor may affect the results of these scans and the imaging exams may affect the electrocardiogram (ECG) data collected by the Zio® XT Monitor.

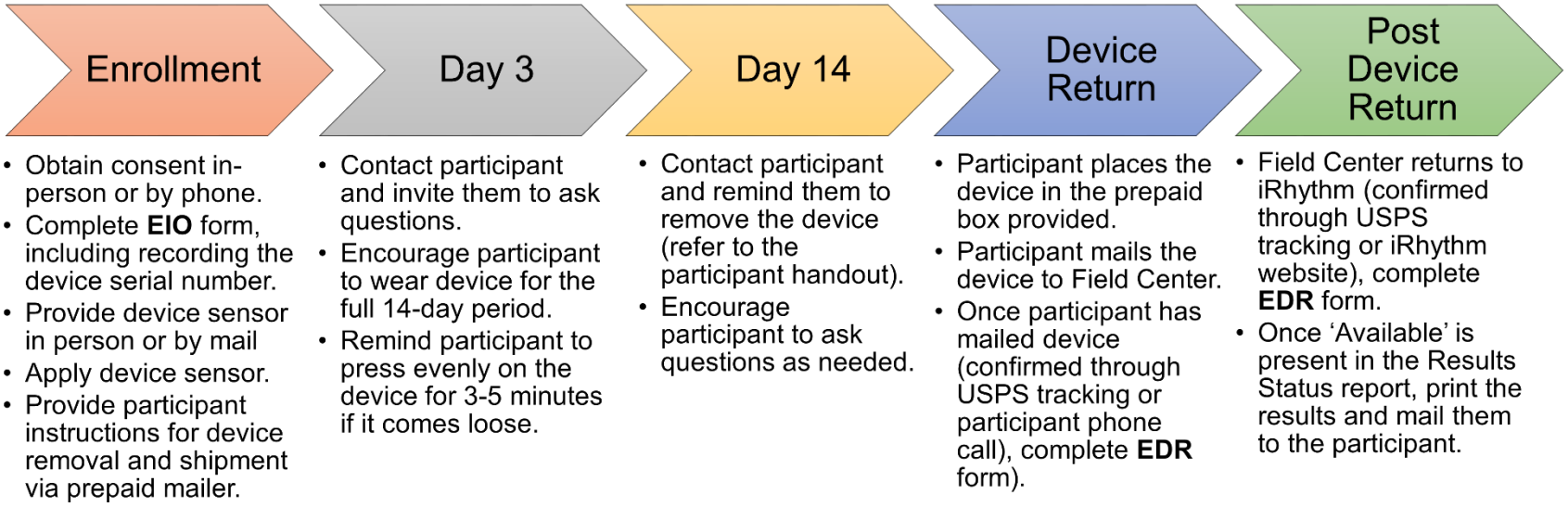
To apply the Zio® XT Monitor, participants will need to remove their upper body clothing. Women do not need to remove their bras.

The participant can shower or exercise as normal while wearing the Zio® XT Monitor but should not swim or bathe as the monitor is water-resistant but not waterproof. Note that showering is not recommended within the first 24 hours after monitor placement.

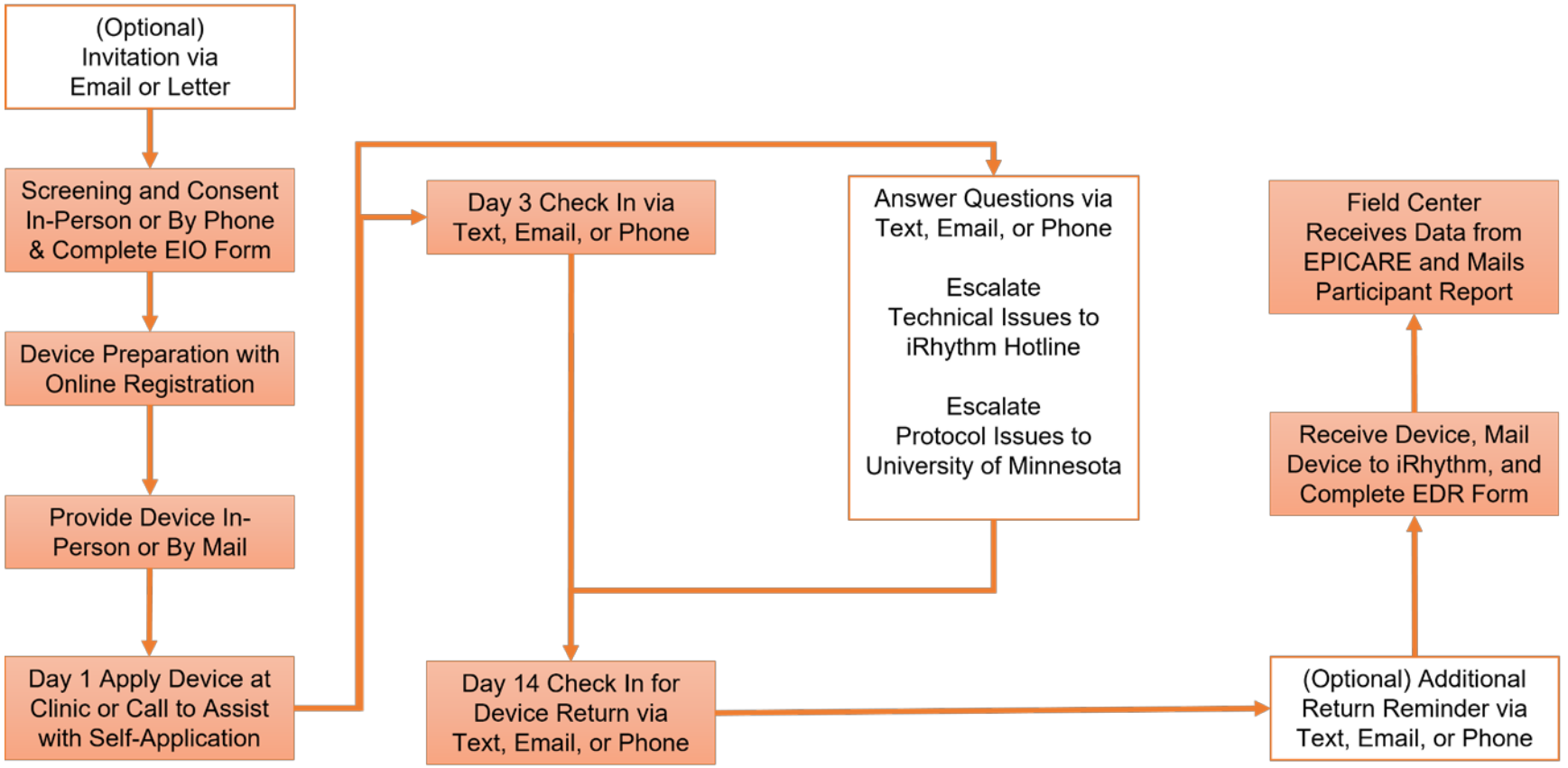
The Zio® XT Monitor kit contains a pre-paid shipping box for the Field Centers to return a device to iRhythm Technologies. **As a result, another pre-paid mailer is to be provided to the participant so that they can return the monitor to the field center**. Refer to the timeline and flowcharts below for an overview of reporting requirements during the 2-week wear period. Day 1 is the day the Zio® XT Monitor is applied to the participant.

On average, the process of obtaining consent and applying the Zio® XT Monitor will take 15 to 20 minutes.

7.1. Protocol Timeline and Flowcharts



Staff Sequence

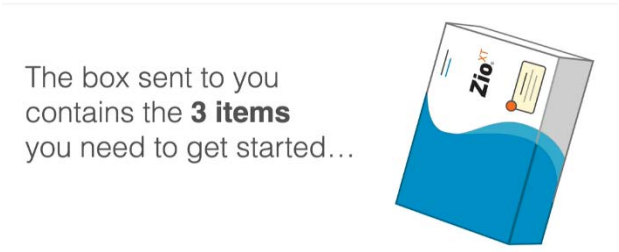


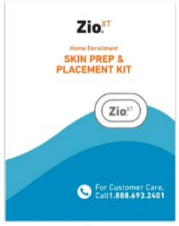
7.2 Equipment, Materials, and Supplies

- Zio® XT Monitor Kit (box serves as Field Center mailer, participant requires another)
- Zio® XT Patient Application Instructions within Zio® XT Monitor Kit (includes template)
- Participant consent forms and handouts (see “Materials provides to participant” below)

The Zio® XT Monitor Kit contains the following:

- 1 Zio® XT Patch
- 1 Skin Prep & Placement Kit, including:
  - 1 Safety Razor
  - 1 Abrader Scrub Pad
  - Alcohol Wipes – used to remove excess skin oil
- Zio® XT Subject Instructions for Zio® XT Monitor removal and return to iRhythm Technologies
- The Zio® XT Monitor Kit box has the iRhythm Technologies return label attached for Field Center mail back.





Materials provided to participant:

- Zio® XT Monitor Kit box with the iRhythm Technologies return label attached, includes Subject Instructions for Zio® XT Monitor removal and return to iRhythm Technologies
- Consent form without signature pages if consent obtained over the phone
- Verbal Consent Handout if consent obtained over the phone

- Participant Handout
- Frequently Asked Questions

If proxy consent is required, materials should be mailed to the proxy.

7.3 Procedures for Registering the Zio® XT Monitor
FC staff will register the Zio® XT Monitor in the Zio® XT Monitor portal (https://www.ziosuite.com) and record the Zio® XT Monitor serial number in the **EIO form** in CDART prior to application of the monitor (see **iRhythm Registration Checklist**). The Zio® XT Monitor serial number can be found on the back of the Zio® XT Monitor, and the outside of the Skin Prep & Placement Kit (3 stickers). One sticker should be affixed to the cover of the Subject Instruction Booklet included in the Zio® XT Monitor kit. When registering the monitor in the Zio® XT Monitor portal, **staff should enter 01/01/1970 for year of birth for all participants**.

The Zio® XT Monitor Kit return box must be labeled with the participant's ARIC ID for processing by iRhythm. The participant pre-paid mailer and Subject Instruction booklet should be labeled with the participant's ARIC ID or a separate code to facilitate tracking. FCs are asked to create their own labels to make it easy to match the monitor to the appropriate participant when the Zio® XT Monitor is returned. Participants should be instructed **not** to add anything to the outside of the box (i.e., a return address with identifying information).

7.4 Procedures for Zio® XT Monitor Application
Application of the Zio® XT Monitor can be viewed here (**see [1] Training Slides, [2] iRhythm produced Training video https://vimeo.com/channels/iRhythmzio**.

1. Position

Locate the Zio card template in the Patient Application Instructions booklet.

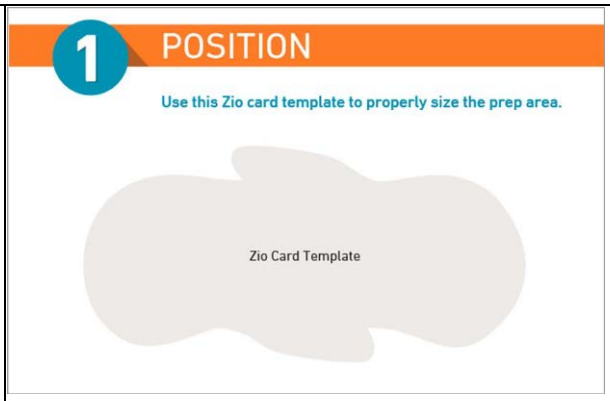
Hold the template to the upper-left side of the subject's chest. It should be on the flattest spot just below the collarbone with the arrow pointing straight up.

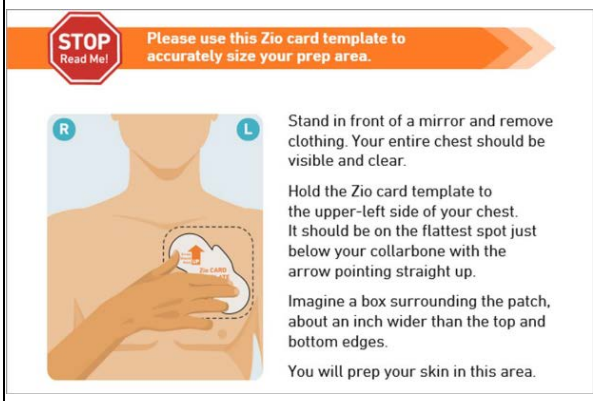
Imagine a box surrounding the patch, about an inch wider than the top and bottom edges.

You will prep the skin in this area.

The Zio® XT Monitor must be placed on bare, hairless skin to allow for adequate contact between the monitor and the body's electrical system. Try not to place the Zio® XT Monitor on skin moles or skin tags.

- **Note: Do not apply any lotions or oils.**





2. Skin preparation

Find the razor in the Skin Prep & Placement Kit.

Hold the sides of the razor packaging with one hand. With the other hand, pull the razor handle to expose the blade.

Shave the area.

Note: Be careful not to shave any moles or skin tags.

Make sure the subject's skin is clean and dry before continuing.

2. Skin preparation (cont'd)

Find the abrader in the Skin Prep & Placement Kit.

Hold the abrader disc by the orange tab.

Rub the abrader in 40 broad strokes across the entire prep area.

Follow the arrows as shown, applying 10 strokes in each direction.

Note: This step is necessary for the monitor to adhere completely and smoothly to the chest and to ensure quality of the recording. Be careful not to abrade any moles or skin tags.

Find the alcohol wipes in the Skin Prep & Placement Kit.

Clean the prep area thoroughly using all alcohol pads.

Let dry for one minute (setting a timer is recommended).

This step is meant to remove excessive skin oil and may feel very warm on subject's skin.

3. Apply Patch

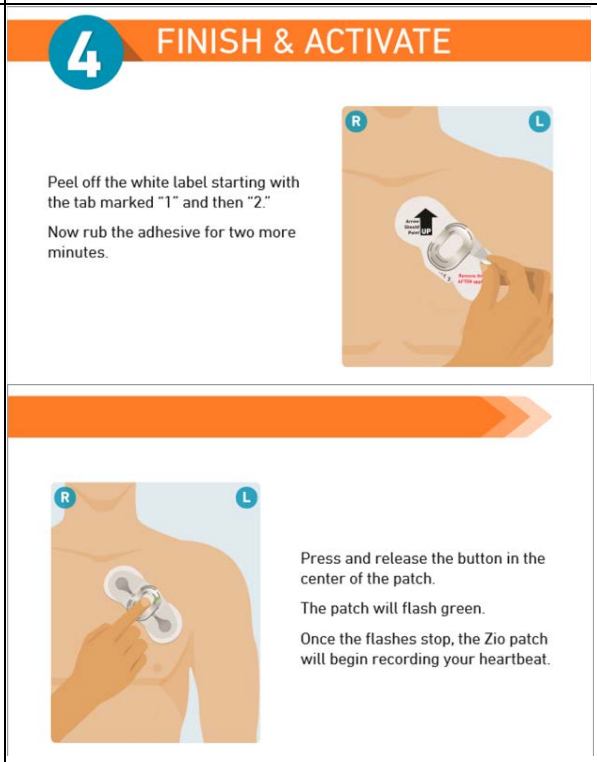
Find the Zio patch in the Skin Prep & Placement Kit.

Hold the middle section of the Zio patch and remove the bottom clear backing.

NOTE: Do not touch the adhesive

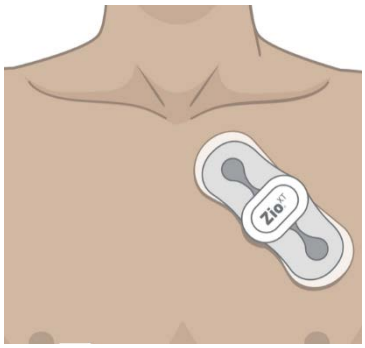
Apply the Zio patch, aiming for the upper-left side of the subject's chest, on the flattest spot just below the collarbone, with the arrow pointing straight up. Then stick the patch on.

Press the Zio patch firmly onto the subject's skin and rub the adhesive for two minutes (setting a timer is recommended).

Do not move the patch after it is applied to the subject's skin.	
4. Finish & Activate Peel off the white label starting with the tab marked "1" and then "2". Rub the adhesive for two more minutes (setting a timer is recommended). Visually inspect the monitor on the participant. If applied properly, the monitor will be completely smooth. There should be no bubbles Press and release the button in the center of the patch. The patch will flash green and will begin recording the subject's heartbeat.	

When employing the phone-based protocol, FC staff will contact the participant and utilize the script in Appendices 5 and 6. Both the in-person and phone-based protocol will use the contact scripts in Appendices 7 and 8. Refer to Frequently Asked Questions at https://sites.cscc.unc.edu/aric/Ziopatch and Appendix 9 for information about variations in the protocol.

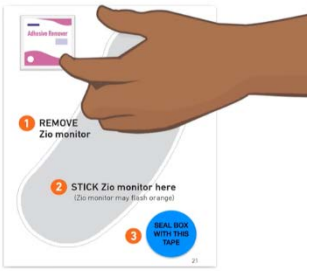
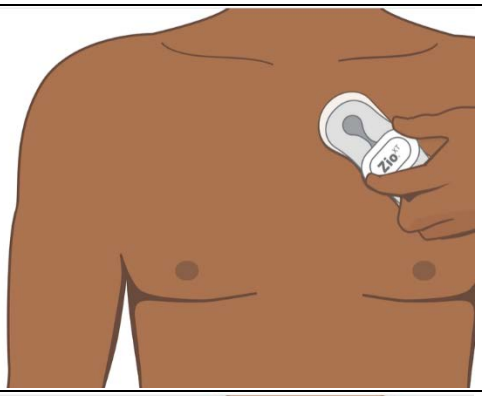
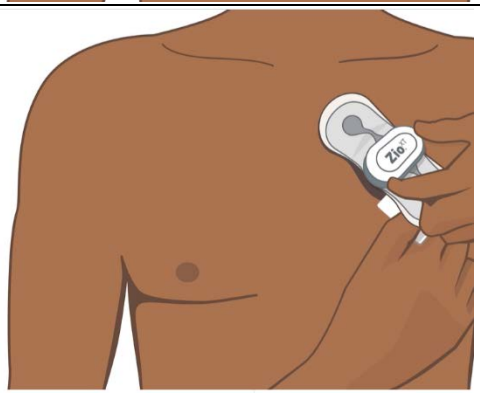
Zio® XT Monitor, the self-adhesive strips, and the placement location.

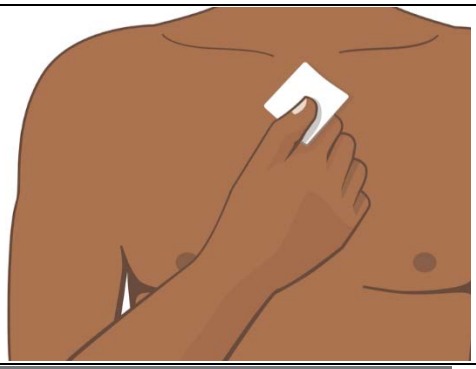


Examples of correct placement of Zio® XT Monitor

7.5 Instructing Participants on Procedures for Zio® XT Monitor Removal
FC staff will provide the participant with the Zio® XT Monitor Participant Handout at https://sites.cscc.unc.edu/aric/Ziopatch, which includes instructions on removal of the monitor. Staff will walk the participant through the steps and answer any questions they may have.

The Participant Handout and Frequently Asked Questions documents include information for participants about what to do if the Zio® XT Monitor falls off early. If this happens, participants or their proxies should contact the FC as soon as possible to replace the monitor. If a replacement device is issued, FC staff will update the sensor number in the **EIO form** for the replacement monitor. Please note that the Zio® XT Monitor will only be replaced if it falls off before Day 3. If the monitor falls off after this, the participant or their proxy may return the monitor early for processing.

1. Find the Symptom Log provided	To remove your Zio, first find your **Symptom Log**. 
2. Take the adhesive remover off the back page before attempting to remove your Zio® XT Monitor	Take the **adhesive remover** off the back page. 
3. Gently lift your Zio® XT Monitor up from the center	Gently **lift your Zio up** from the center. 
4. Using the adhesive remover, peel from the center out, one side at a time	Using the remover, **peel from the center out**, one side at a time. 

5. Do not attempt to remove your Zio® XT Monitor without the adhesive remover	**Do not attempt** to remove your Zio without the Adhesive Remover. 
6. Wash your skin with mild soap, rinse with water, and pat dry	Wash your skin with mild soap, rinse with water, and pat dry.
7. Attach your Zio® XT Monitor to the last page of your Symptom Log	**Stick** your Zio to the last page of your **Symptom Log**. 
8. Use the blue sticker to seal your return box	Take the **blue sticker** off. You'll use it to seal your return box. 

7.6 Procedures for Returning the Zio® XT Monitor to iRhythm Technologies

On Day 14, ARIC staff will contact participants or proxies to remind participants to remove and return the Zio® XT Monitor to the field center. Staff will then return the device to iRhythm using the pre-paid and labeled return box. Please ensure that the return box is labeled with the participant's ARIC Subject ID before returning the device to iRhythm.

Two business days after Day 14, begin tracking the monitor return using the USPS (*not* UPS) tracking number or via iRhythm's website. Use the ARIC-AMP Monitor Return Report to check for devices that have passed the expected return date. If the Zio® XT Monitor has not been mailed 5 business days after Day 14, contact the participant to remind him/her to return the monitor to the field center.

Once the device has been marked as mailed, it will continue to appear in the ARIC-AMP Monitor Return Report until a Reviewer form (**form code: EDX**) has been entered.

7.7 Data Transfer

When the Zio® XT Monitor is returned to iRhythm Technologies, iRhythm Technologies will upload the Zio® XT Monitor standard report data onto the secure iRhythm Portal (https://www.ziosuite.com). The standard report includes a cover page summarizing the main arrhythmia diagnoses and ECGs of the arrhythmias. The latter will allow verification of reported arrhythmias. Each Zio® XT Monitor standard report will be identified by an ARIC ID recorded in CDART. No participant identifiers will be available to iRhythm.

An EPICARE Reviewer will download this report from the iRhythm website and then upload it into the **EDX form** in CDART. The reviewer will then verify the Zio® XT Monitor serial number in the report against the serial number that is automatically applied in the **EDX form**. In the case of a mismatch, the reviewer should notify the Coordinating Center (CC) and the Field Center about any discrepancies. The reviewer, FC, and CC will work to resolve each discrepancy on a case-by-case basis.

Once the serial number has been verified, the Reviewer will review the iRhythm standard report and enter any abnormal or alert findings into the **EDX form** in CDART.

7.8 ECG Quality Assurance

Several procedures are in place to monitor data quality. General feedback pertaining to all FC staff will be provided during regular conference calls with FC study coordinators.

All ECG scans will be reviewed for recording quality by EPICARE. This information is recorded in a spreadsheet that will be included with regular summary data transfers to the CC by EPICARE.

8. Participant Safety

Clinics will be staffed with on-site healthcare professionals trained to ensure participants' comfort and safety. We do not anticipate any adverse events from the procedures of this ancillary study. Healthcare professionals will be available in case of any unexpected or unusual medical events. Serious adverse events will be reported to the CC, the single IRB (sIRB), local IRBs, and the Observational Study Monitoring Board (OSMB) within 5 days of the event or as prescribed by specific guidelines. Minor adverse events and unanticipated problems will be tracked and reported to the OSMB on a semi-annual basis. The OSMB will provide oversight of study progress and safety. Serious adverse events, minor adverse events, and unanticipated problems must be entered into CDART according to the protocol described in ARIC Manual 2.

8.1 Skin Irritations

Occasionally itchy skin known as pruritus (proo-rie'-tus) can occur when the skin comes in contact with certain materials or chemicals. This can be uncomfortable and produce a sensation

which makes one want to scratch. It can produce what is called irritant contact dermatitis which can be more painful than itchy and appear as a rash, redness, or bumps on the skin which may be mild, progress to a more severe reaction or in some cases an allergic reaction.

An allergic reaction is an abnormal response of the immune system to a normally harmless substance. In this situation the body may react to the substance as if it *were* harmful. Allergic skin reactions (or allergic contact dermatitis) can cause hives (red, itchy, raised areas of the skin), angioedema (swelling of the skin), or eczema (a more chronic inflammation of the skin) which can produce a red, scaly itchy rash.

Tips for managing skin reactions from contact with substances include:

1. Avoid the offending substance or material.
2. Keep the skin clean and dry without scrubbing it or using harsh chemicals like rubbing alcohol on it.
3. Use over the counter preparations that soothe and cool the skin. Lotions, gels and creams may be kept in the refrigerator which can help with the soothing affect they may provide.
4. Nonprescription corticosteroid cream or topical anesthetics used temporarily may relieve an itch that involves inflamed skin.

If simple approaches do not help and/or it is felt an allergic reaction is present it is best to consult a dermatologist for more definitive diagnosis and treatment.

As with any unexpected event experienced in relation to being a participant in this study, individuals enrolled in ARIC-AMP should be encouraged to contact FC staff and report a concern as soon as it becomes problematic for them. If the participant has an uncomfortable reaction to wearing the device (e.g., skin irritation, redness, slight swelling, itching, burning), they may choose to withdraw from the study. This decision is up to the participant who may confer with FC staff as needed.

8.2 Results Reporting

Following the 14-day sensor wear period, participants will be notified if there were any heart rhythm abnormalities or alerts that may require medical attention. The data are typically processed by iRhythm 5 to 7 days after the device is placed in the mail by the participant. The processed data is reviewed by EPICARE within 1 to 2 days. Consequently, a report should appear in CDART 1 to 2 weeks after the device is mailed.

Each ARIC participant that agreed to receive results will receive a written report, either by regular mail or email depending on their preference documented in the consent form. Along with the iRhythm standard report cover page, the participant will receive a summary results letter based on 1 of 3 templates: (1) “no abnormal findings”, (2) “abnormal findings present”, or (3) “alerts present”. Refer to https://sites.cscc.unc.edu/aric/Ziopatch for participant letters.

Dr. Elsayed Soliman and his team of physician ECG readers in EPICARE (Wake Forest University) will download the standard report from the iRhythm Portal daily. They will verify the accuracy of heart rhythm findings in the iRhythm standard report. Dr. Elsayed Soliman and the EPICARE staff will decide which letter should be sent to each participant and enter this decision in the **EDX form**. They will also upload the iRhythm standard report into CDART as an attachment to the **EDX form**.

Dr. Soliman's team will review the Zio® XT Monitor reports for any potentially life-threatening arrhythmias that require alert notification. In addition, iRhythm staff will immediately report any potentially life-threatening arrhythmias they discover to Dr. Soliman and his team in EPICARE who will verify that the alerts are correct. For all alert findings, Dr. Soliman will immediately enter the alert notification and upload the iRhythm standard report onto CDART. Dr. Soliman will send an email to FC PIs or designated FC physician, FC staff, and Dr. Chen to notify them of the alert. FC PIs or physicians will contact participants within 24 to 48 hours to discuss the alert findings and recommend to participants to discuss the findings with a physician.

On the same day, FC staff will prepare a results letter and a physician letter and send it with the full iRhythm standard report (including ECG tracing) by FedEx overnight mail to the participant. If requested, these materials will also be provided to a physician directly. Refer to https://sites.cscc.unc.edu/aric/Ziopatch for physician letters.

FCs will check the ARIC-AMP Results Status Report in CDART at least weekly for participant results from EPICARE. Assuming the participant has consented to receive results, FC staff will send the ARIC summary of results letters along with the cover page of the iRhythm standard report to the participant. If requested, the FC will also send a copy of the results letter, iRhythm standard report, and the relevant physician cover letter to the participant's physician.

Participant reports that do not contain an alert may be sent in batches along with the other results sent to the participant, such as lab results, activity reports, etc. Reports with abnormal results should be sent at least weekly and reports with normal results should be sent at least bi-weekly. Reports may be sent by regular mail or email depending on the preferences indicated by the participant in the consent form.

8.3 Potential Abnormal Findings and Alerts

The definitions of abnormal findings and alerts are provided below. Letters for each type of finding and alert are available at https://sites.cscc.unc.edu/aric/Ziopatch.

Abnormal findings

- Atrial fibrillation
- Atrial flutter
- Supraventricular ectopy (SVE)/Premature atrial contractions (PACs) – state only if >1%
- Supraventricular couplets – state only if >1%
- Supraventricular triplets – state only if >1%
- Supraventricular tachycardia
    - If a single episode is >30 seconds
    - If on average, >1 episode per day
- Ventricular ectopy (VE)/Premature ventricular contractions (PVCs) – state only if >1%
- Ventricular couplets – state only if >1%
- Ventricular triplets – state only if >1%
- Non-sustained ventricular tachycardia
    - If a single episode is >15 seconds and ≤30 seconds
    - If on average, >1 episode per day
- 2nd degree AV block, Mobitz I (AV Wenckebach)
- Paced beats (should be very rare since having an implantable device is an exclusion criterion)

Alerts

- Wide QRS tachycardia >120 bpm and sustained for >30 seconds (includes monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, ventricular fibrillation)
- Complete heart block
- 2nd degree AV Block, Mobitz II
- Pause >6 seconds
- Bradycardia <40 bpm and sustained for >30 seconds
- Atrial fibrillation/atrial flutter with average heart rate <40 bpm or >180 bpm and sustained for 60 seconds
- Narrow QRS tachycardia >180bpm and sustained for 60 seconds

EPICARE may in some instances report other abnormalities or alert findings if deemed appropriate.

Abnormality or Alert	Description in Letter
Atrial fibrillation	This is an irregular heart rhythm. It may feel like palpitations or "racing heart beats".
Atrial flutter	This is a fast rhythm that originates from the upper chambers of the heart. It may feel like palpitations or "racing heart beats".
Supraventricular ectopy (SVE) / Premature atrial contractions (PACs) / Supraventricular bigeminy / Supraventricular trigeminy / Supraventricular couplets / Supraventricular triplets	These are heartbeats that come early and originate from the upper chambers of the heart. They may feel like palpitations or "skipping a beat".
Supraventricular tachycardia	This is a fast rhythm that originates from the upper chambers of the heart. It may feel like palpitations or "racing heart beats".
Ventricular ectopy (VE) / Premature ventricular contractions (PVCs) / Ventricular bigeminy / Ventricular trigeminy / Ventricular couplets / Ventricular triplets	These are heartbeats that come early and originate from the lower chambers of the heart. They may feel like palpitations or "skipping a beat".
Non-sustained ventricular tachycardia	This is a fast rhythm that originates from the lower chambers of the heart. It may feel like palpitations or "racing heart beats".
2nd degree AV block, Mobitz I (AV Wenckebach)	This is an occasional slowing of heart rate due to a drop of a beat in the lower chambers.
Paced beats	These are heart beats that originate from a pacemaker device rather than your heart's own pacemaker.
Wide QRS tachycardia >120 bpm and sustained for >30 seconds (includes monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, ventricular fibrillation)	This is a fast rhythm that originates from the lower chambers of the heart and may feel like palpitations or "racing heart beats".
Complete heart block	This is a slow heart beat due to an interruption in the electrical pathway in the heart.
2nd degree AV Block, Mobitz II	This is a slow heart beat due to an interruption in the electrical pathway in the heart.
Pause >6 seconds	There was no heartbeat for 6 seconds or longer.
Bradycardia <40 bpm and sustained for >30 seconds	This is a slower than usual heart rate that lasted more than 30 seconds.
Atrial fibrillation/atrial flutter with average heart rate <40 bpm or >180 bpm and sustained for 60 seconds	This is an irregular heart rhythm. It may feel like palpitations or "racing heart beats".
Narrow QRS tachycardia >180bpm and sustained for 60 seconds	This is a fast rhythm that originates from the upper chambers of the heart. It may feel like palpitations or "racing heart beats".

Abnormal Report – Ventricular Tachycardia, Atrial Fibrillation and Pause

Zio XT

Zio XT Final Report for

Report, Patient #16

iRhythm Technologies
Tel: (888) 693-2401
www.zioreports.com

iRhythm

Date of Birth	Patient ID	Gender	Primary Indication (R94.31)
12/12/67 (51 yrs)		Female	Abnormal electrocardiogram

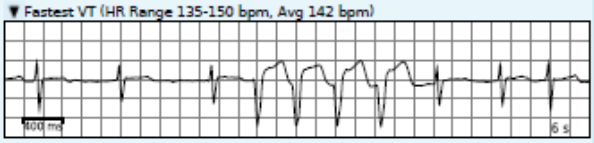
Prescribing Clinician	Managing Location
Dr. E. Physician	San Francisco

Enrollment Period	Analysis Time
13 days 19 hours 03/22/19, 05:24am to 04/05/19, 12:40am	13 days 19 hours (after artifact removed)

Ventricular Tachycardia (4 beats or more)

Episodes: **5**
HR Range: **116-150 bpm**
Avg: **132 bpm**

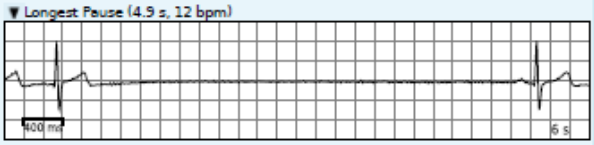
▼ Fastest VT (HR Range 135-150 bpm, Avg 142 bpm)



Pauses (3 secs or longer)

Episodes: **3**
Range: **3.9-4.9 s**

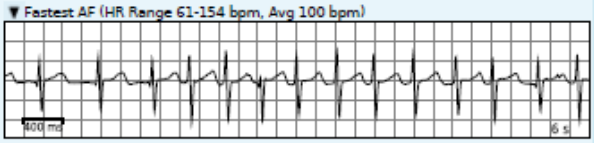
▼ Longest Pause (4.9 s, 12 bpm)



Atrial Fibrillation

AF Burden: **37%**
Longest Duration: **1 d 19 h**
HR Range: **50-154 bpm**
Avg: **97 bpm**

▼ Fastest AF (HR Range 61-154 bpm, Avg 100 bpm)



AV Block (2nd° Mobitz II, 3rd°)

None found

Supraventricular Tachycardia (4 beats or more)

None found

Heart Rate

Overall	Max	**154 bpm**	09:49am, 03/25
	Min	**50 bpm**	11:59pm, 03/22
	Avg	**78 bpm**	
Sinus	Max	**96 bpm**	11:14am, 03/24
	Min	**50 bpm**	11:59pm, 03/22
	Avg	**66 bpm**	

Patient Events

Total Triggers: 2 **Total Diaries: 1**

Findings within ± 45 sec of triggered events or diary entries:

	Range	Trigger	Diary
AF	59-126 bpm	✓	✓
Pause(s)	3.9 s	✓	
Sinus	56-73 bpm	✓	
SVE(s)		✓	
VE(s)			✓

Ectopics

	Rare <1%	Occasional 1% to ≤5%	Frequent >5%
Supraventricular Ectopy (SVE/PACs)			
Isolated	**Rare**	<1.0%	6723
Couplet	**Rare**	<1.0%	141
Triplet	**Rare**	<1.0%	9
Ventricular Ectopy (VE/PVCs)			
Isolated	**Rare**	<1.0%	1716
Couplet	**Rare**	<1.0%	192
Triplet	**Rare**	<1.0%	26

Longest Ventricular Bigeminy Episode	0 s
Longest Ventricular Trigeminy Episode	0 s

Preliminary Findings

Patient had a min HR of 50 bpm, max HR of 154 bpm, and avg HR of 78 bpm. Predominant underlying rhythm was Sinus Rhythm. 5 Ventricular Tachycardia runs occurred, the run with the fastest interval lasting 4 beats with a max rate of 150 bpm, the longest lasting 4 beats with an avg rate of 127 bpm. Episodes of Ventricular Tachycardia may be possible Atrial Fibrillation with aberrancy. Atrial Fibrillation occurred (37% burden), ranging from 50-154 bpm (avg of 97 bpm), the longest lasting 1 day 19 hours with an avg rate of 97 bpm. 3 Pauses occurred, the longest lasting 4.9 secs (12 bpm). Atrial Fibrillation and Pause were detected within +/- 45 seconds of symptomatic patient event(s). Isolated SVEs were rare (<1.0%, 6723), SVE Couplets were rare (<1.0%, 141), and SVE Triplets were rare (<1.0%, 9). Isolated VEs were rare (<1.0%, 1716), VE Couplets were rare (<1.0%, 192), and VE Triplets were rare (<1.0%, 26).

Final Interpretation

1. Agree with above interpretation
2. Underlying Sinus rhythm with normal rates average =78/min
3. 5 runs of VT some of which could be AF with aberrancy
4. Atrial fibrillation with 37% burden and longest run of 42 hours
5. Pauses of up to 4.9 seconds likely post conversion related
6. Triggered events consistent with AF, Pauses

Electronically signed by Dr. Example Physician 04/12/19 06:18 PM (CT)
SIGNATURE

Appendix 1: Contact Information

FC staff can direct questions to the following individuals, depending on the topic area and question:

- Email Janet Flores at janet.flores@iRhythmtech.com with technical questions related to the Zio® XT Monitor.
- Email Sue Greimel at moone104@umn.edu with general questions related to the protocol, such as results notification.

Lead Center PI:

- University of Minnesota: Dr. Lin Yee Chen chenx484@umn.edu

To order additional Zio® XT Monitors, FC staff should email Sue Greimel (moone104@umn.edu) and copy Lin Yee Chen (chenx484@umn.edu) and Niki Oldenburg (olden019@umn.edu). **Sites should contact Sue Greimel, Lin Yee Chen, and Niki Oldenburg about ordering more monitor when they have 10 monitors left.**

Appendix 2: COVID-19 Safety Protocol

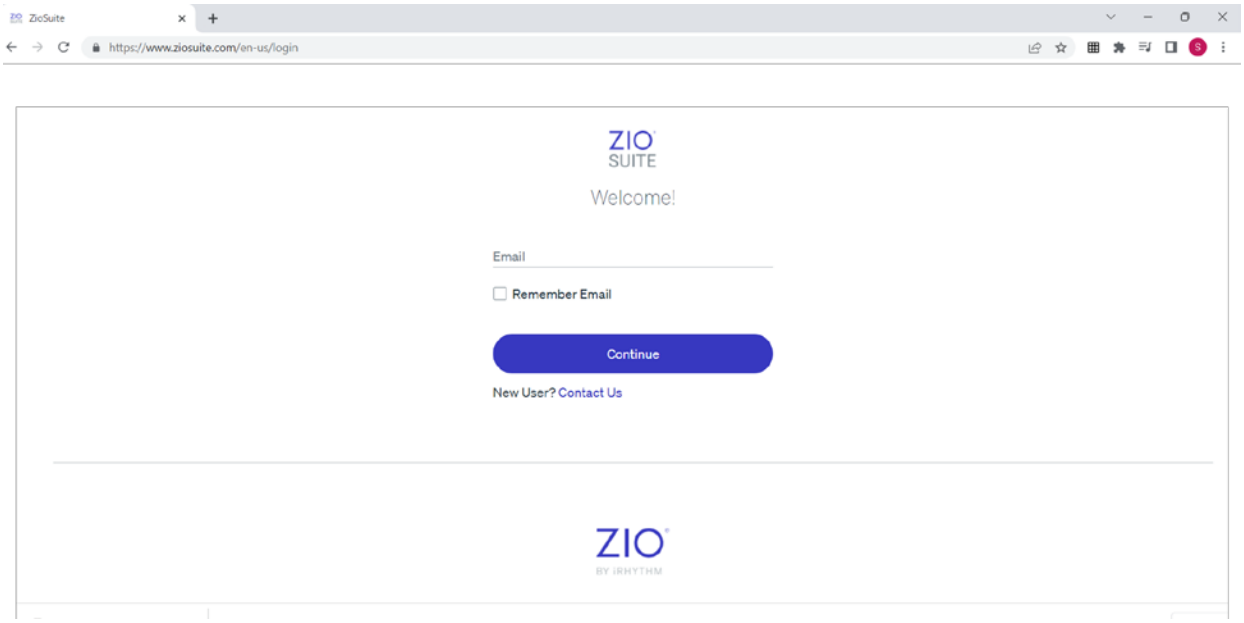
FC staff are expected to follow local institutional policies regarding COVID-19. The FCs must inform the Lead Center (LC) of ongoing changes to institutional COVID-19 safety protocols to help preserve the integrity of the study protocol. Please refer to the appendix of ARIC Manual 2 for additional information about COVID-related protocols that will be implemented in ARIC Visit 11.

If the local risk of COVID-19 infection is of concern, FC staff may obtain informed consent remotely and mail the device to the participant. In either case, no special sanitization procedures are required for the device.

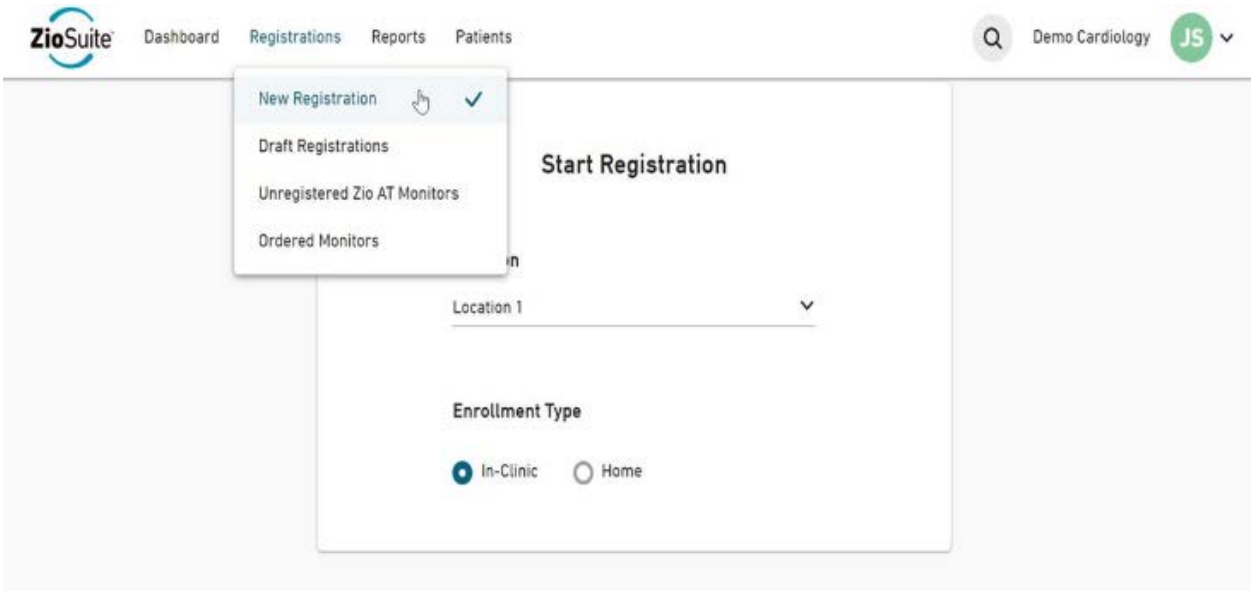
Individual	Suggested Procedure	Suggested Frequency	Suggested Product(s)
Staff	- Wear surgical mask and other personal protective equipment. - Wash hands and use hand sanitizer.	Before, during, and after each in-person session.	- Surgical Mask - Hand sanitizer
ARIC-AMP participants	- Wear surgical mask or other face covering.	Before and after each in-person session.	- Mask

Appendix 3: Zio® XT Monitor Portal Enrollment Instructions

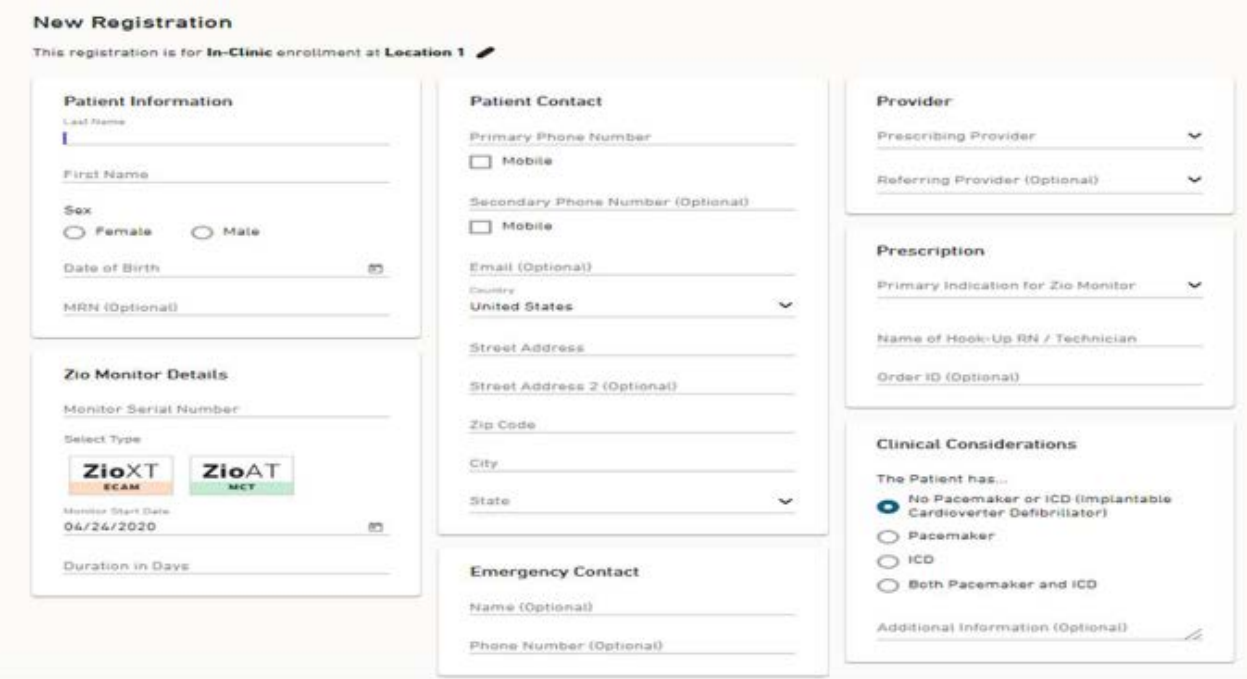
Log-in to ZioSuite (www.ZioSuite.com) using your email address and individual password.



1. Select the “Registration” tab in the header menu and then select “New Registration”. Enter your location (Forsyth, Jackson, Minnesota, or Washington) and select In-Clinic for the Enrollment Type (regardless of whether the patch is applied in person or mailed). Note: The “Dashboard” tab provides monitor and report status, while the “Reports” tab provides access to patient reports (view/save in PDF format), and the “Patients” tab allows viewing of all registered patients at the selected site.


ZioSuite
Dashboard
Registrations
Reports
Patients
Demo Cardiology
JS
New Registration
Draft Registrations
Unregistered Zio AT Monitors
Ordered Monitors
Start Registration
Location 1
Enrollment Type
In-Clinic
Home

2. You will now see the Subject Enrollment screen.



Required Fields:
-Last Name: Enter ARIC ID#.
-First Name: Enter ARIC ID#.
-Sex: Enter Male
-Date of Birth: Enter 01/01/1970.
- Primary Phone Number: Enter your site's phone number.
-Street Address/Zip Code/City/State: Enter your site's address.
-Enter the Zio® XT Monitor Device Number. The monitor serial number can be found on the back of the Zio® XT Monitor, on the Skin Prep & Placement Kit package, and on the cover of the Subject Instruction Booklet included in the Zio® XT Monitor kit (affixed by FC staff).
-Select the ZioXT Device Type.
-Monitor Start Date: Enter today's date in MM/DD/YYYY format.
-Duration in Days: Enter 14.
- Prescribing Provider: Select your FC Principal Investigator.
-Primary Indication for Zio Monitor: Select Z13.6 Encounter for screening for cardiovascular disorders
-Under Clinical Considerations, indicate that the Patient has No Pacemaker or ICD (Implantable Cardioverter Defibrillator).

After all required information is entered, select “Complete Registration”. If information is missing or the process can’t be completed at this time, select the “Save As Draft” option and return later (selecting “Draft Registrations” from the Registration pull-down menu).

Appendix 4: Checklists

Overall Zio® XT Monitor Checklist for In-Person Protocol

In clinic

- ☐ Assess eligibility
- ☐ Complete **EIO form**
- ☐ Enroll participant in the Zio® XT Monitor portal
- ☐ Apply Zio® XT Monitor to participant
- ☐ Provide printed materials and answer any questions
- ☐ Day 1 is the day Zio® XT Monitor is applied to participant

Day 3 Zio® XT Monitor Protocol

- ☐ Ask whether participant is still wearing Zio® XT Monitor
  - o If not, ask participant/proxy if they would be willing to try again with a replacement monitor. If so, schedule visit to FC or mail monitor replacement. Participant may directly apply replacement monitor and notify staff if they do not want to be guided through the process again over the phone.
- ☐ Clarify any questions
- ☐ Encourage participant to wear the Zio® XT Monitor for the full 14 days. The device may be removed on the 14th day.

Day 14 Zio® XT Monitor Protocol

- ☐ Ask whether participant is still wearing Zio® XT Monitor
  - o If so, ask participant/proxy to remove the Zio® XT Monitor and return it to iRhythm Technologies in the mailer provided.
  - o If not, ask the participant/proxy if they have already returned the device to iRhythm Technologies
  - o If they have, thank them.
  - o If they have not, please ask them to return the Zio® XT Monitor to iRhythm Technologies in the mailer provided
- ☐ Clarify any questions

Receipt of Zio® XT Monitor

- ☐ Use the ARIC-AMP Monitor Return Report to facilitate tracking of returns. Participant may be compensated once the Zio® XT Monitor is returned.
- ☐ Five business days after Day 14, if the Zio® XT Monitor has not been mailed contact the participant/proxy to remind him/her to return the monitor to the field center. Continue to follow-up every 5 business days until the monitor is mailed (confirmed by USPS tracking number) or received by the field center.
- ☐ If monitor is deemed lost in the mail, contact iRhythm (Janet Flores, janet.flores@iRhythmtech.com).
- ☐ Document return date in the **EDR form.**

Results Reporting and Alert Notification

- ☐ Check the ARIC-AMP Results Status Report in CDART weekly for determination of (1) normal results, (2) abnormal results, and (3) alerts. For (3) alerts, EPICARE will also send email to FC PI, FC physician, and FC staff.
- ☐ For (1) and (2) mail cover letter plus cover page of iRhythm standard report
- ☐ For (3) overnight mail cover letter plus entire iRhythm standard report AND ask the FC PI or physician to contact the participant/proxy

Other Issues

- For support regarding Zio® XT Monitor, contact iRhythm (Janet Flores, janet.flores@iRhythmtech.com)
- For questions regarding project, contact Project Manager (Sue Greimel, moone104@umn.edu)

Overall Zio® XT Monitor Checklist for Phone Protocol

Remotely

- ☐ Assess eligibility
- ☐ Complete **EIO form**
- ☐ Enroll participant in the Zio® XT Monitor portal
- ☐ Label Zio® XT Monitor kit with participant's ARIC ID
- ☐ Label participant pre-paid mailer with Field Center specific ID and mail to participant/proxy along with printed materials

Day 1 Zio® XT Monitor Protocol

- ☐ Contact participant to confirm receipt of device
- ☐ Guide participant/proxy on application of the Zio® XT Monitor using Patient Application Instructions as needed
- ☐ Day 1 is the day Zio® XT Monitor is applied to participant

Day 3 Zio® XT Monitor Protocol

- ☐ Ask whether participant is still wearing Zio® XT Monitor
  - o If not, ask participant/proxy if they would be willing to try again with a replacement monitor. If so, schedule visit to FC or mail monitor replacement. Participant may directly apply replacement monitor and notify staff if they do not want to be guided through the process again over the phone.
- ☐ Clarify any questions
- ☐ Encourage participant to wear the Zio® XT Monitor for the full 14 days. The device may be removed on the 14th day.

Day 14 Zio® XT Monitor Protocol

- ☐ Ask whether participant is still wearing Zio® XT Monitor
  - o If so, ask participant/proxy to remove the Zio® XT Monitor and return it to iRhythm Technologies in the mailer provided. .
  - o If not, ask the participant/proxy if they have already returned the device to iRhythm Technologies
  - o If they have, thank them.
  - o If they have not, please ask the participant/proxy to return the Zio® XT Monitor to iRhythm Technologies in the mailer provided
- ☐ Clarify any questions

Receipt of Zio® XT Monitor

- ☐ Use the ARIC-AMP Monitor Return Report to facilitate tracking of returns. Participant may be compensated once the Zio® XT Monitor is returned.
- ☐ Five business days after Day 14, if the Zio® XT Monitor has not been mailed, contact the participant/proxy to remind him/her to return the monitor to iRhythm Technologies. Continue to follow-up every 5 business days until the monitor is mailed (confirmed by USPS tracking number) or received by iRhythm.
- ☐ If monitor is deemed lost in the mail, contact iRhythm (Janet Flores, janet.flores@iRhythmtech.com)
- ☐ Document return date in the **EDR form**

Results Reporting and Alert Notification

- ☐ Check the ARIC-AMP Results Status Report in CDART weekly for determination of (1) normal results, (2) abnormal results, and (3) alerts. For (3) alerts, EPICARE will also send email to FC PI, FC physician, and FC staff
- ☐ For (1) and (2) mail cover letter plus cover page of iRhythm standard report
  For (3) overnight mail cover letter plus entire iRhythm standard report AND ask the FC PI or physician to contact the participant/proxy

Other Issues

- For support regarding Zio® XT Monitor, contact iRhythm (Janet Flores, janet.flores@iRhythmtech.com)
- For questions regarding project, contact Project Manager (Sue Greimel, moone104@umn.edu)

Appendix 5: Script for Phone Protocol

Please Note: ARIC Cohort participants should not be contacted via text. ARIC Generation 2 participants can be contacted via text.

Receipt of Mailed Device Text to Participant [For Gen2 participants only]

This is [*staff name*] from the ARIC study checking to see if you received your heart monitor. Please let us know as soon as possible so we can assist with self-application.

Receipt of Mailed Device Call to Participant

If you are speaking to an answering machine □ Hello, this is [*staff name*] and I am calling from the ARIC study to speak with [*participant first and last name*]. [*Participant name*], we are calling to see if you received your heart monitor. Please contact us at your earliest convenience so we can assist with self-application. We can be reached by phone at [*FC phone number*] or by email at [*FC email address*]. Thank you and we look forward to hearing from you soon.

If a person is reached □ Hello, may I speak with [*participant name*]?

> **If participant is UNAVAILABLE** □ *Ask when you may call back to speak with [participant name].*
>
> **If participant is AVAILABLE** □ Hello, this is [*staff name*] and I am calling from the ARIC study to talk with you about your heart monitor.

1. Have you received your heart monitor?

YES □ Great, thank you. *Go to Question 2.*

NO □ Would you please contact us when you receive your heart monitor?

> **YES** □ Great, we look forward to hearing from you!
>
> **NO** □ That's fine. We'll contact you again in a few days.

2. Is now a good time for me to assist you with applying the heart monitor?

YES □ Great. *Go to Question 3.*

NO □ *Schedule a time with participant to call and assist with application. Skip to Question 8.*

3. Do you have the following from the kit provided to you?

- Patient Application Instructions
- Subject Instructions
- Safety Razor
- Abrader Scrub Pad
- Alcohol Wipes
- Heart Monitor

YES □ *Go to Question 4.*

NO □ *Help participant locate each item. Lost or misplaced items can be sent in the mail.*

4. Please stand in front of a mirror and remove your shirt. Using the information on pages 6 through 11 of the Patient Application Instructions, can you prepare the area where you will apply the Heart Monitor by doing the following?

- Shaving the area with the safety razor.
- Abrading the area with the abrader scrub pad. You should make 10 strokes diagonally from top left to bottom right, 10 strokes diagonally from top right to bottom left, 10 strokes horizontally, and 10 strokes vertically.
- Cleaning the area with alcohol wipes.
- Waiting 1 minute.

YES □ *Walk through each step with the participant. Once participant has prepared the application area and one minute has passed, go to Question 5.*

NO □ *Provide additional instructions to guide the participant as necessary.*

5. Using the information on pages 12 and 13 of the Patient Application Instructions, can you apply the Heart Monitor by doing the following?

- Removing the clear backing from the monitor.
- Applying the monitor on the upper left side of chest on the flattest spot just below the collarbone with the arrow pointing straight up. When doing this, be careful not to touch the adhesive.
- Pressing the patch firmly and rubbing the adhesive for 2 minutes. Do not move the patch after it is applied.

YES □ *Walk through each step with the participant. Use a timer to time 2 minutes for the last step. Once participant has applied the Heart Monitor, go to Question 6.*

NO □ *Provide additional instructions to guide the participant as necessary.*

6. Using the information on page 14 of the Patient Application Instructions, can you activate the Heart Monitor by doing the following?

- Peeling off the white label “1”.
- Peeling off the white label “2”.
- Rubbing the adhesive for 2 more minutes.

YES □ *Walk through each step with the proxy. Use a timer to time 2 minutes for the last step. Once participant has activated the Heart Monitor, go to Question 7.*

NO □ *Provide additional instructions to guide the participant as necessary.*

7. Now press and release the button in the center of the patch as shown on page 15. Is the patch flashing green?

YES □ Great, the patch is recording your heartbeat. *Go to Question 8.*

NO □ *The device is faulty. Ask the participant to remove the device by following the steps in the Subject Instructions. The faulty device can be placed in the labeled return box and mailed. If the participant is willing, a replacement device can be sent to them in the mail and the process can be repeated.*

8. Do you have any questions about the heart monitor?

YES □ *Troubleshoot with participant. Refer to list of frequently asked questions with responses. Continue to Closing.*

NO □ *Continue to Closing.*

Closing
Please remember to wear the heart monitor for 2 weeks. We will contact you again in 3 days. If you have any questions while wearing the Heart Monitor, please reach out to us. Thank you for agreeing to have [*participant name*] participate in this study.

Please Note: ARIC Cohort participants should not be contacted via text. ARIC Generation 2 participants can be contacted via text.

Receipt of Mailed Device Text to Proxy [For Gen2 participants only]

This is [*staff name*] from the ARIC study checking to see if you received [*participant name*]'s heart monitor. Please let us know as soon as possible so we can assist with application.

Receipt of Mailed Device Call to Proxy

If you are speaking to an answering machine □ Hello, this is [*staff name*] and I am calling from the ARIC study to speak with [*proxy first and last name*]. [*Proxy name*], we are calling to see if you received [*participant name*]'s heart monitor. Please contact us at your earliest convenience so we can assist with application. We can be reached by phone at [*FC phone number*] or by email at [*FC email address*]. Thank you and we look forward to hearing from you soon.

If a person is reached □ Hello, may I speak with [*proxy name*]?

Proxy is UNAVAILABLE □ *Ask when you may call back to speak with* [*proxy name*].

Proxy is AVAILABLE □ Hello, this is [*staff name*] and I am calling from the ARIC study to talk with you about [*participant first and last name*]'s heart monitor.

1. Have you received the heart monitor?

YES □ Great, thank you*. Go to Question 2.*

NO □ Would you please contact us when you receive the heart monitor?

YES □ Great, we look forward to hearing from you!

NO □ That's fine. We'll contact you again in a few days.

2. Is now a good time for me to assist you with applying the heart monitor on [*participant name*]?

YES □ Great. *Go to Question 3.*

NO □ *Schedule a time with participant to call and assist with application.*

3. Do you have the following from the kit provided to you and [*participant name*]?

- Patient Application Instructions
- Subject Instructions
- Safety Razor
- Abrader Scrub Pad
- Alcohol Wipes
- Heart Monitor

YES □ *Go to Question 4.*

NO □ *Help proxy locate each item. Lost or misplaced items can be sent in the mail.*

4. Using the information on pages 6 through 11 of the Patient Application Instructions, can you prepare the area on [*participant name*] where you will apply the Heart Monitor by doing the following?

- Shaving the area with the safety razor.
- Abrading the area with the abrader scrub pad. You should make 10 strokes diagonally from top left to bottom right, 10 strokes diagonally from top right to bottom left, 10 strokes horizontally, and 10 strokes vertically.
- Cleaning the area with alcohol wipes.
- Waiting 1 minute.

YES □ *Walk through each step with the proxy. Once proxy has prepared the application area and one minute has passed, go to Question 5.*

NO □ *Provide additional instructions to guide the proxy as necessary.*

5. Using the information on pages 12 and 13 of the Patient Application Instructions, can you place the Heart Monitor on [*participant name*] by doing the following?

- Removing the clear backing from the monitor.
- Applying the monitor on the upper left side of chest on the flattest spot just below the collarbone with the arrow pointing straight up. When doing this, be careful not to touch the adhesive.
- Pressing the patch firmly and rubbing the adhesive for 2 minutes. Do not move the patch after it is applied.

YES □ *Walk through each step with the proxy. Use a timer to time 2 minutes for the last step. Once proxy has applied the Heart Monitor, go to Question 6.*

NO □ *Provide additional instructions to guide the proxy as necessary.*

6. Using the information on page 14 of the Patient Application Instructions, can you activate the Heart Monitor by doing the following?

- Peeling off the white label “1”.
- Peeling off the white label “2”.
- Rubbing the adhesive for 2 more minutes.

YES □ *Walk through each step with the proxy. Use a timer to time 2 minutes for the last step. Once participant has activated the Heart Monitor, go to Question 7.*

NO □ *Provide additional instructions to guide the proxy as necessary.*

7. Now press and release the button in the center of the patch as shown on page 15. Is the patch flashing green?

YES □ Great, the patch is recording [*participant name*]’s heartbeat. *Go to Question 8.*

NO □ *The device is faulty. Ask the proxy to remove the device by following the steps in the Subject Instructions. The faulty device can be placed in the labeled return box and mailed. If the proxy and the participant are willing, a replacement device can be sent to them in the mail and the process can be repeated.*

8. Do you have any questions about the heart monitor?

YES □ *Troubleshoot with proxy. Refer to list of frequently asked questions with responses. Continue to Closing.*

NO □ *Continue to Closing.*

Closing
Please remember to have [*participant name*] wear the heart monitor for 2 weeks. We will contact you again in 3 days. If you or [*participant name*] have any questions while [*participant name*] is wearing the Heart Monitor, please reach out to us. Thank you for agreeing to have [*participant name*] participate in this study.

Appendix 6: Scripts for 3-Day, 14-Day, & Retrieval Calls and Texts

Reminder Scripts for Participant

Please Note: ARIC Cohort participants should not be contacted via text. ARIC Generation 2 participants can be contacted via text.

3-Day Text [For Gen2 participants only]

This is [*staff name*] from the ARIC study making sure you're still wearing your heart monitor. If you have any issues or questions, please let us know.

3-Day Call

If you are speaking to an answering machine □ Hello, this is [*staff name*] and I am calling from the ARIC study to speak with [*participant first and last name*]. [*Participant name*], we are calling to see if you are wearing your heart monitor. If you have questions, please contact us at your earliest convenience. We can be reached by phone at [*FC phone number*] or by email at [*email address*]. Thank you and we look forward to hearing from you soon.

If a person is reached □ Hello, may I speak with [*participant name*]?

> **If participant is UNAVAILABLE** □ *Ask when you may call back to speak with* [*participant name*].
>
> **If participant is AVAILABLE** □ Hello, this is [*staff name*] and I am calling from the ARIC study to talk with you about your heart monitor.

1. Are you still wearing the heart monitor?

YES □ Great, thank you. *Go to Question 2.*

NO □ Are you willing to try again?

> **YES** □ Would you prefer to come in to have the heart monitor applied by our staff, or to have the heart monitor mailed to you? If we mail the heart monitor to you, we can contact you a few days afterward to guide you with the application of the monitor.
>
> *Schedule an in-person appointment or mail another device (following registration of serial number), according to the participant's preference. Start a new occurrence of EDR to record information for the new device.*
>
> **NO** □ Please put the heart monitor in the labeled return box and mail it. Thank you for participating in this study.

2. Do you have any questions about the heart monitor?

YES □ *Troubleshoot with participant. Refer to list of frequently asked questions with responses. Continue to Closing.*

NO □ *Continue to Closing.*

Closing
Please continue to wear the heart monitor for 2 weeks. We will contact you again in 11 days. If you have any questions while wearing the heart monitor, please reach out to us. Thank you for participating in this study. ***End call.***

Please Note: ARIC Cohort participants should not be contacted via text. ARIC Generation 2 participants can be contacted via text.

14-Day Text [For Gen2 participants only]

This is [*staff name*] from the ARIC study reminding you to remove your heart monitor and return it in the pre-paid mailer. If you have any issues or questions, please let us know.

14-Day Call

If you are speaking to an answering machine □ Hello, this is [*staff name*] and I am calling from the ARIC study to speak with [*participant first and last name*]. We are calling to remind you to remove your heart monitor and return it in the pre-paid mailer. If you have questions about your heart monitor, please contact us at your earliest convenience. We can be reached by phone at [*FC phone number*] or by email at [*email address*]. Thank you for participating in this study.

If a person is reached □ Hello, may I speak with [*participant name*]?

> **If participant is UNAVAILABLE** □ Ask when you may call back to speak with [*participant name*].
>
> **If participant is AVAILABLE** □ Hello, this is [*staff name*] and I am calling from the ARIC Study to talk with you about your heart monitor.

1. Are you still wearing the heart monitor?

YES □ Great. Please remove the heart monitor now and put it in the labeled return box and mail it. *Go to Question 2*.

NO □ Have you returned the heart monitor using the labeled return box?

> **YES** □ Great. *Continue to Closing*.
>
> **NO** □ Please put the heart monitor in the labeled return box and mail it. *Go to Question 2*.

2. Do you have any questions?

NO □ *Continue to Closing.*

YES □ *Troubleshoot with participant. Refer to list of frequently asked questions with responses. Continue to Closing.*

Closing
Thank you for participating in this study. ***End call.***

Retrieval Reminders

- ☐ 5 business days after Day 14: first retrieval contact
- ☐ 5 business days after first retrieval contact: second retrieval contact
- ☐ Repeat above until participant returns heart monitor by mail

Please Note: ARIC Cohort participants should not be contacted via text. ARIC Generation 2 participants can be contacted via text.

Retrieval Text [For Gen2 participants only]

This is [*staff name*] from the ARIC study with a friendly reminder to return your heart monitor in the pre-paid mailer. If you have any issues or questions, please let us know.

Retrieval Call

If you are speaking to an answering machine □ [*Participant name*], we are calling to see if you have returned your heart monitor. It can be placed directly in the box provided and dropped in the mail. If you have any questions or concerns, please contact us at your earliest convenience. We can be reached by phone at [*FC phone number*], or by email at [*email address*]. Thank you for participating in this study.

If a person is reached □ Hello, may I speak with [*participant name*]?

> **If participant is UNAVAILABLE** □ Ask when you may call back to speak with [*participant name*].
>
> **If participant is AVAILABLE** □ Hello, this is [*staff name*] and I am calling from the ARIC study to talk with you about your heart monitor.

Have you returned the heart monitor using the labeled return box?

YES □ Great, thank you for participating in this study. ***End call.***

NO □ Please put the heart monitor in the labeled return box and mail it. ***End call.***

Reminder Scripts for Proxy

Please Note: ARIC Cohort participants should not be contacted via text. ARIC Generation 2 participants can be contacted via text.

3-Day Text [For Gen2 participants only]

This is [*staff name*] from the ARIC study making sure that [*participant name*] is still wearing their heart monitor. If you have any issues or questions, please let us know.

3-Day Call

If you are speaking to an answering machine □ Hello, this is [*staff name*] and I am calling from the ARIC study to speak with [*proxy first and last name*]. [*Proxy name*], we are calling to see if [*participant name*] is wearing their heart monitor. If you or [*participant name*] have questions, please contact us at your earliest convenience. We can be reached by phone at [*FC phone number*] or by email at [*email address*]. Thank you and we look forward to hearing from you soon.

If a person is reached □ Hello, may I speak with [*proxy name*]?

If proxy is UNAVAILABLE □ *Ask when you may call back to speak with* [*proxy name*].

If proxy is AVAILABLE □ Hello, this is [*staff name*] and I am calling from the ARIC study to talk with you about [*participant name*]'s heart monitor.

1. **Is [*participant name*] still wearing the heart monitor?**

YES □ Great, thank you. *Go to Question 2.*

NO □ Are you willing to have [*participant name*] try again?

YES □ Would you prefer for [*participant name*] to come in to have the heart monitor applied by our staff, or to have the heart monitor mailed to you to apply on [*participant name*]? If we mail the heart monitor to you, we can contact you a few days afterward to guide you with the application of the monitor.

Schedule an in-person appointment or mail another device (following registration of serial number), according to the proxy's preference. Start a new occurrence of EDR to record information for the new device.

NO □ Please put the heart monitor in the labeled return box and mail it. Thank you for agreeing to have [*participant name*] participate in this study.

2. Do you or [*participant name*] have any questions about the heart monitor?

YES □ *Troubleshoot with proxy. Refer to list of frequently asked questions with responses. Continue to Closing.*

NO □ *Continue to Closing.*

Closing
Please continue to have [*participant name*] wear the heart monitor for 2 weeks. We will contact you again in 11 days. If you or [*participant name*] have any questions while they are wearing the heart monitor, please reach out to us. Thank you for agreeing to have [*participant name*] participate in this study. ***End call.***

Please Note: ARIC Cohort participants should not be contacted via text. ARIC Generation 2 participants can be contacted via text.

14-Day Text [For Gen2 participants only]
This is [*staff name*] from the ARIC study reminding you to have [*participant name*] remove their heart monitor and return it in the pre-paid mailer. If you have any issues or questions, please let us know.

14-Day Call
If you are speaking to an answering machine □ Hello, this is [*staff name*] and I am calling from the ARIC study to speak with [*proxy first and last name*]. We are calling to remind you to have [*participant name*] remove their heart monitor and return it in the pre-paid mailer. If you or [*participant name*] have questions about the heart monitor, please contact us at your earliest convenience. We can be reached by phone at [*FC phone number*] or by email at [*email address*]. Thank you for participating in this study.

If a person is reached □ Hello, may I speak with [*proxy name*]?

> **If proxy is UNAVAILABLE** □ Ask when you may call back to speak with [*proxy name*].
>
> **If proxy is AVAILABLE** □ Hello, this is [*staff name*] and I am calling from the ARIC Study to talk with you about [*participant name*]'s heart monitor.

1. Is [*participant name*] still wearing the heart monitor?

YES □ Great. Please remove the heart monitor now and put it in the labeled return box and mail it. *Go to Question 2.*

NO □ Have you returned the heart monitor using the labeled return box?

> **YES** □ Great. *Continue to Closing.*
>
> **NO** □ Please put the heart monitor in the labeled return box and mail it. *Go to Question 2.*

2. Do you have any questions about the heart monitor?

NO □ *Continue to Closing.*

YES □ *Troubleshoot with proxy. Refer to list of frequently asked questions with responses. Continue to Closing.*

Closing
Thank you for agreeing to have [*participant name*] participate in this study. ***End call.***

Retrieval Reminders

- ☐ 5 business days after Day 14: first retrieval contact
- ☐ 5 business days after first retrieval contact: second retrieval contact
- ☐ Repeat above until participant returns heart monitor by mail

Please Note: ARIC Cohort participants should not be contacted via text. ARIC Generation 2 participants can be contacted via text.

Retrieval Text [For Gen2 participants only]

This is [*staff name*] from the ARIC study with a friendly reminder to return [*participant name*]'s heart monitor in the pre-paid mailer. If you have any issues or questions, please let us know.

Retrieval Call

If you are speaking to an answering machine □ [*Proxy name*], we are calling to see if you have returned [*participant name*]'s heart monitor. It can be placed directly in the box provided and dropped in the mail. If you have any questions or concerns, please contact us at your earliest convenience. We can be reached by phone at [*FC phone number*], or by email at [*email address*]. Thank you for agreeing to have [*participant name*] participate in this study.

If you are speaking to an answering machine □ Hello, may I speak with [*proxy name*]?

> **If proxy is UNAVAILABLE** □ Ask when you may call back to speak with [*proxy name*].
>
> **If proxy is AVAILABLE** □ Hello, this is [*staff name*] and I am calling from the ARIC study to talk with you about [*participant name*]'s heart monitor.

Have you returned the heart monitor using the labeled return box?

YES □ Great, thank you for agreeing to have [*participant name*] participate in this study. ***End call.***

NO □ Please put the heart monitor in the labeled return box and mail it. ***End call.***

Appendix 7: Zio® XT Monitor Recruitment and Wear Outcomes and Form Actions

Outcome	Actions
The participant is eligible but declines participation in ARIC-AMP.	1. Open the **EIO form** and catalog the reason why the participant declined participation.
The participant has schedule conflicts but agrees to future participation in ARIC-AMP.	1. Find out from participant a good date to contact for a re-screen. This should be a date on which no travel, X-rays or other medical scans are scheduled for at least the following two weeks. Do not assign a monitor to the participant. 2. Contact the participant on the scheduled date and re-administer screening. 3. With each subsequent recruitment attempt, the **EIO form** should be used and updated to reflect the most recent attempt. 4. Continue recruitment attempts until the participant can have the Zio® XT Monitor placed OR the participant does not agree to future participation in ARIC-AMP.
The participant has the Zio® XT Monitor successfully placed. The self-adhesive monitor is removed at the end of the 14-day wear period.	1. Ask participant to return Zio® XT Monitor to the field center. 2. Complete the **EDR form** when Zio® XT Monitor is returned to the field center. 3. Once results have been uploaded to CDART by EPICARE as indicated via the ARIC-AMP Results Status Report in CDART, either email or print and mail the PDF results and cover letter to the participant and their physician if requested.
The participant has the Zio® XT Monitor successfully placed. The self-adhesive monitor is removed **after day 3** but before day 14 of the 14-day wear period is complete.	1. Ask participant to return Zio® XT Monitor to the field center. 2. Complete the **EDR form** when Zio® XT Monitor is returned to the field center. 3. Once results have been uploaded to CDART by EPICARE as indicated via the ARIC-AMP Results Status Report in CDART, either email or print and mail the PDF results and cover letter to the participant and their physician if requested.
The participant has the Zio® XT Monitor successfully placed. The self-adhesive monitor is removed **on or before day 3** of the 14-day wear period. The participant **agrees** to replace the monitor.	1. Contact as soon as possible to replace the monitor either in-person or by mail. The monitor can be replaced as many times as the participant is willing to re-apply the device. 2. If participant prefers remote application, mail a replacement monitor and instruct participant on procedures for replacing themselves. This will include notifying staff when the device has been received and applied. 3. **Begin a new occurrence** of the **EDR form** for the replacement device. The 14-day wear period starts again from Day 1 when the replacement device is applied. 4. Complete the **EDR form** when the replacement Zio® XT Monitor is returned to the field center. 5. Once results have been uploaded to CDART by EPICARE as indicated via the ARIC-AMP Results Status Report in CDART, either email or print and mail the PDF results and cover letter to the participant and their physician if requested.
The participant has the Zio® XT Monitor successfully placed. The self-adhesive monitor is removed **on or before day 3** of the 14-day wear period is complete. The participant **does not agree** to replace the monitor.	1. Ask participant to return Zio® XT Monitor to the field center. 2. Complete the **EDR form** when Zio® XT Monitor is returned to the field center. 3. Once results have been uploaded to CDART by EPICARE as indicated via the ARIC-AMP Results Status Report in CDART, either email or print and mail the PDF results and cover letter to the participant and their physician if requested.