Manual 21
Zio Patch Procedures
ARIC-NCS Visit 6 Study Protocol

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Title: Significance of Atrial Fibrillation and Atrial Fibrillation Burden Detected by Novel ECG Monitoring in Community-Dwelling Elderly
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A. SPECIFIC AIMS

Aim 1: In elderly ARIC participants, we will use a 2-week ambulatory Zio®XT Patch monitor to define the prevalence of subclinical AF and AF burden, and identify subgroups with high prevalence of subclinical AF.

Aim 2: Assess the association of (a) markers of atherosclerosis with AF and AF burden on ECG monitor in older age, (b) modifiable atherosclerotic risk factors over the previous 30 years (V1:1987-1989 to V5:2011-2013) with AF and AF burden on ECG monitor in older age.

Aim 3: Quantify the relationship of AF burden in the elderly to risk of (a) composite of nonfatal ischemic stroke, nonfatal myocardial infarction, heart failure hospitalization, and CV death, and (b) cognitive decline or dementia.

B. METHODS

Study population

We will apply the Zio®XT Patch to all consenting participants returning for the ARIC Visit 6 (V6) exam. For participants in nursing homes or assisted living facilities, we will consider **ARIC staff-application** by home visits (first choice) or mailing the device to participants for **self-application** (second choice). Participants must be able to mail the device back to iRhythm Technologies, Inc. (the company).

Exclusion criteria: History of skin allergic reactions to adhesive tape or inability to mail the device back to iRhythm.

Participants who took part in the ARIC Holter study (Jackson, Forsyth) or who have had other rhythm tests by their physicians are still eligible.

If it is anticipated that a participant will not be able to complete 2 weeks of monitoring (e.g., MRI exam in a few days, participant will be out of the country, etc.), consider applying the patch on another day when 2 weeks of continuous monitoring will be possible.

Study procedures

Application by ARIC staff

Participants returning for the V6 exam will be invited to participate in the proposed project, which includes wearing the Zio® XT Patch for 2 weeks and keeping a symptom diary. A brief questionnaire (**ZIO**) will take 5 minutes. Registration of the participant on the iRhythm website (see **iRhythm Registration Checklist**) and application of the Zio® XT Patch to the participants' left upper chest will take 10-15 minutes (**see [1] Training Slides, [2] Training video https://vimeo.com/channels/irhythmzio**). Participants will need to remove their upper body clothing; women do not need to remove their bra. The questionnaire will elicit information on prior diagnosis of AF**.** A trigger button, integrated into the monitor's design, can be activated to create a digital time stamp on the continuously recorded data stream to synchronize the recorded ECG rhythm with symptoms. Participants will be instructed to activate the trigger should they experience any suspected symptom of arrhythmia (palpitations, irregular heart beat sensation, "skipped beat" sensation, chest discomfort, dizziness, and fainting) and to document the symptoms in a symptom diary. This will enable determination of whether recorded arrhythmias are symptomatic or asymptomatic (see **Participant Enrollment Checklist**). Day 1 is the day the Zio® XT Patch is applied to the participant.

On Day 3, ARIC staff will call participants to answer any questions and to encourage participants to wear the device for as long as possible. On Day 10, ARIC staff will call participants to remind them to return the Zio® XT Patch and symptom diary to iRhythm (see **Day 3 and Day 10 Phone Script**). The symptom diary also contains some FAQs and instructions on how to remove the Zio® XT Patch (see **Appendix**). At the end of the application period, participants will mail the device back to iRhythm using a pre-paid and labeled return box.

If V6 participants prefer to delay their wearing of the Zio® XT Patch until a later date, they can have it applied then, or if need be, apply the Zio® XT Patch themselves.

Self-application

For participants who decline the Zio® XT Patch during the V6 clinic exam, we will apply the Zio® XT Patch during home visits. If a home visit is not possible but a participant wants to take part, we have the option of mailing the device to participants for self-application. If the participant opts for self-application at home, instruct the participant to call the Field Center when he/she receives the Zio® XT Patch so that Field Center staff can assist with self-application by telephone. The registration date on the iRhythm website and the start date of the patch monitor will be the date that the Zio® XT Patch is mailed out (see **iRhythm Registration Checklist**).

ARIC staff will first conduct the 5-minute questionnaire (**ZIO**). Next, the participant will apply the device to the left upper chest using simple written instructions and assisted by telephone support from ARIC staff (**see [1] Training Slides, [2] Training video https://vimeo.com/channels/irhythmzio**). Participants will be instructed to activate the trigger should they experience any suspected symptom of arrhythmia and to document the symptoms in a symptom diary. On Day 3, ARIC staff will call participants to answer any questions and to encourage participants to wear the device for as long as possible. On Day 10, ARIC staff will call participants to remind them to return the Zio® XT Patch and symptom diary to iRhythm (see **Day 3 and Day 10 Phone Script**). At the end of the application period, participants will mail the device back to iRhythm using a pre-paid and labeled return box.

Results reporting

A standard report will be generated by iRhythm and will be uploaded to a secure iRhythm website. 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 Patch device will be identified by an ARIC study ID and no participant identifiers will be available to iRhythm. **Appendix** includes an example of an iRhythm standard report.

Dr. Elsayed Soliman and his team of physician ECG readers in EPICARE (Wake Forest University) will download the standard report from the iRhythm website on a daily basis. They will verify the accuracy of heart rhythm findings in the iRhythm standard report. All ARIC participants will receive an ARIC summary results letter that will be 1 of 3 template letters: (1) “no abnormal findings”, (2) “abnormal findings present”, or (3) “alerts present”. Dr. Elsayed Soliman and the EPICARE staff will decide which template letter should be sent to each participant and this decision will be entered into a secure website (CDART). The iRhythm standard report will also be uploaded onto CDART. The Coordinating Center and Field Centers will have access to EPICARE’s decision on the template letter and the iRhythm standard report via CDART. ARIC Field Center staff will then prepare the ARIC summary results letters and send it with the cover page of the iRhythm standard report to participants, and with participants’ permission, their physicians. If a participant had previously participated in the Holter Study, we will also include the findings of the Holter study in the summary results letter. If a participant requests for the iRhythm standard report to be sent to his/her physician, we will send the physician the full iRhythm standard report, including the ECG tracings.

The definitions of abnormal findings and alerts are provided in the **Appendix**. The **Appendix also** shows the template ARIC summary results letters for “no abnormal findings”, “abnormal findings present”, or “alerts present”.

Alert notification

Every day, Dr. Soliman’s team will review the Zio®XT Patch reports for any potentially life-threatening

arrhythmias that will require alert notification. In addition, potentially life-threatening arrhythmias that are discovered by iRhythm staff will be immediately reported 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 also send an email to ARIC Field Center PIs, Field Center staff, and the project PI, Dr. Chen to notify them of the alert. Field center PIs or physicians will call participants to discuss the alert findings and recommend to participants to discuss the alert findings with their physicians.

In addition, on the same day that the alert was reported, ARIC Field Center staff will prepare the ARIC summary results letters and send it with the full iRhythm standard report (including ECG tracings) by FedEx to participants, and with participants' permission, their physicians.

Retrieval phone calls

Eight (8) business days after Day 14, check the iRhythm website for availability of the standard report. If the report is available, send check to the participant. If the report is not available, call the participant (first phone call) to remind him/her to return the Zio®XT Patch to iRhythm if he/she has not returned the Zio®XT Patch. If the participant has returned the Zio®XT Patch, stop calling the participant.

Check the website 8 business days after the first phone call. If the report is not available, call the participant again (second phone call) to remind him/her to return the Zio®XT Patch to iRhythm if he/she has not returned the Zio®XT Patch. If the participant has returned the Zio®XT Patch, stop calling the participant. Check the website 8 business days after the second phone call and repeat the above until participant returns the Zio®XT Patch by mail.

If a certain time interval has passed and it is clear that the patch monitor is lost in the mail, email the project PI, Dr. Chen.

Maximizing participation

Participant reimbursement

Participants will be reimbursed $25 when the iRhythm standard report is available on the iRhythm website.

Appointment reminder script

During the Visit 6 appointment reminder call, the Zio®XT Patch opportunity will be explained briefly, so that participants are expecting it. To encourage participation, including participation from those who have completed the Holter study (R1R01HL116900-01A1), we will include the following sentences in the phone script:

"This ARIC visit includes a heart rhythm monitor study, which we encourage you to participate in. The heart rhythm monitor is a small patch that looks like a band-aid. This patch has no wires or cables and will be applied to the left chest. You will wear it continuously for 2 weeks and can still perform your daily activities such as showering and exercising. At the end of the 2-week period, you will mail back the device using a pre-paid return box. We ask that you please wear to the clinic a top that is easily removed (women: to your bra) to allow staff to apply the patch monitor."

{Answer to, "Why do I want to do another heart monitoring study?"
"By monitoring your heart rhythm over a longer period of 2 weeks, we may be able to identify additional heart rhythm findings."}

{Answer to, "I already know I have an arrhythmia or atrial fibrillation or pacemaker."
"By monitoring your heart rhythm over a period of 2 weeks, we will be able to determine the frequency or how much arrhythmia or atrial fibrillation that you have. Depending on the type or setting of your pacemaker, heart rhythm abnormalities may not be captured by your pacemaker."}

Clinic scripts
The Zio®XT Patch study is included in the consent form for participants to decide whether they want to take part or not. The staff administering consent will mention that it will add 15 minutes to the exam and require them to wear the Zio®XT Patch for 2 weeks, but in return they will receive some reimbursement and information about whether arrhythmias are detected.

When the main Visit 6 components are completed and it is time for the Zio®XT Patch, the staff will say, "The next item is to apply the heart monitor and give you instructions about it. This will take about 15 minutes."

If a participant who had consented is now unwilling to stay for another 15 minutes, the staff will ask:

"Would you be willing to come in again another day for this patch monitor?" If "YES", we will schedule an appointment for the participant to return for the application of the Zio®XT Patch. If "NO", consider whether staff could go to the home. If "NO", staff will ask:

"We can also mail this patch monitor to you. We will call you in a few days afterward to guide you with the application of the patch monitor. Is this OK?"

Falls ancillary study (R56 AG0459886)
Since the patch monitor imposes minimal burden to participants, we should enroll participants concurrently into both the Zio®XT Patch and Falls ancillary studies. In fact, it would be ideal to have participants wear both the Zio®XT Patch and accelerometer simultaneously which will provide the opportunity to correlate physical activity levels with heart rhythm abnormalities.

C. INFORMED CONSENT

The following statements should be added to the consent form;

Under procedures, below Sensor Test:

"Heart monitor. You will be asked to wear a patch on the upper chest that records information on any irregular heartbeats you may have. You will be asked to wear this patch for up to 2 weeks and return it by mail for interpretation by experts."

Under risks:
"The heart monitor patch may cause minor skin irritation when it is placed on the skin."

Under benefits:
"The heart monitor can provide potentially useful information about any heart rhythm abnormalities that you may have."

D. WEARING THE Zio®XT PATCH TWICE FOR A TOTAL DURATION OF 4 WEEKS

This change in protocol will involve all field centers except for Forsyth County.

During V6, moving forward, for every consecutive participant without known AF from ARIC ascertainment or V6 ZIO questionnaire, we will offer 2 Zio XT Patches to participant

- First Zio XT Patch: apply in clinic. Participant will bring home the second Zio XT Patch.
    - Day 3 and Day 10 phone calls for first Zio XT Patch (as per current protocol)

- Second Zio XT Patch: After 14 days, participant will remove first Zio XT Patch and mail the Zio XT Patch to iRhythm (as per current protocol). About 4-5 days later, field center staff will call participant to assist applying the second Zio XT Patch
    - Day 3 and Day 10 phone calls for second Zio XT Patch
- Second Zio XT Patch: To provide flexibility with scheduling, participants can also wear the second Zio XT patch up to 1 month after the first patch.
- It is not a problem if participant wears the first Zio XT Patch for <14 days. Number of days worn for first Zio XT Patch does not preclude proceeding to second Zio XT Patch.
- Participants will be reimbursed $50 for wearing the Zio XT Patch for 4 weeks.
- If a participant declines wearing the Zio XT patch for 4 weeks, we will offer to participant to wear for 2 weeks.

ZIO forms

Each Zio XT Patch will have his own unique ZIO form. It is important to fill out the serial number and date of application in the ZIO form for the second Zio XT Patch.

On the day that the second Zio XT patch is applied, it is important to register the patch on the iRhythm website and fill out the ZIO form.

Results reporting

For each Zio XT Patch, please send the first page of the iRhythm report together with the cover letter to participants, and with participants' permission, their physicians.

When and How to Return Patch Monitor

- Wear for 14 days
- After 14 days, remove patch monitor and insert patch monitor together with button press log booklet into box that has "ZIO^{XT}" on it
- Drop the box into the nearest mail box

When and How to Return Patch Monitors

- Wear first patch monitor for 14 days

- After 14 days, remove first patch monitor and insert patch monitor together with button press log booklet into box that has "ZIO^{XT}" on it
- Drop the box into the nearest mail box

- After 4 days, call xxx (xxx-xxx-xxxx) to get help in putting on second patch monitor

- Wear second patch monitor for 14 days

- After 14 days, remove second patch monitor and insert patch monitor together with button press log booklet into box that has "ZIO^{XT}" on it

- Drop the box into the nearest mail box