Protocol

Study Official Title: Evaluation of the use of Apple Watch features for identification of cardiac arrythmias

ClinicalTrials.gov Identifier: NCT03769207

Document Date: November 13, 2018

Protocol

Apple Heart Study 1.2

Evaluation of the use of Apple Watch features for identification of cardiac arrhythmias

Protocol Version: 1.14

Protocol Date: November 13, 2018

Sponsor: Apple Inc.
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In collaboration with Stanford Center for Clinical Research (SCCR), Quantitative Sciences Unit (QSU), and Center for Digital Health (CDH).

PROTOCOL APPROVAL PAGE

STUDY TITLE: Apple Heart Study 1.2

Protocol Version: 1.14

Protocol Date: November 13, 2018

This research study will be conducted in the United States, in accordance with applicable parts of 21 CFR Parts 50, 54, and 56.

I, the undersigned, have read and approved this protocol, and agree on its contents.

INVESTIGATORS' SIGNATURE PAGE

STUDY TITLE: Apple Heart Study 1.2

Protocol Version: 1.14

Protocol Date: November 13, 2018

I have read this Study Protocol and agree to adhere to the requirements of this current version of the protocol.

I have not been restricted from participating in clinical research, nor is any action pending that could result in such restriction. If this occurs, I shall provide immediate notification to the Sponsor.

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with applicable parts of 21 CFR Parts 50, 54, and 56, and all governing IRB requirements.

TABLE OF CONTENTS

ACRONYMS

AF - Atrial Fibrillation or Atrial Flutter
AFib - Atrial Fibrillation
CFR - Code of Federal Regulations
EAS - ECG Analysis Set
ECG - Electrocardiography, Electrocardiogram, Electrocardiographic
Apple Watch ECG app-AFib - Apple Watch ECG app classification of atrial fibrillation
EMS - Emergency Medical Services
FAS - Full Analysis Set
FDA - Food and Drug Administration
FOG - Fallout Subgroup
HIPAA - Health Insurance Portability and Accountability Act
HITRUST - Health Information Trust Alliance
HR - Heart Rate
IRN - Irregular Rhythm Notification
IPNA - Irregular Pulse Notification Algorithm
IRB - Institutional Review Board
NAS - Notification Analysis Set
NOC - Network Operating Center
OAC - Oral anticoagulation
OCG - Online Care Group
PCI - Payment Card Industry
PPG - Photoplethysmography, Photoplethysmogram
PPV - Positive Predictive Value
PRO - Patient Reported Outcomes
SAP - Statistical Analysis Plan
SC - Steering Committee

PROTOCOL SYNOPSIS

Study Title	Apple Heart Study 1.2: evaluation of the use of the Apple Watch for identification of cardiac arrhythmias
Protocol Version	1.14
Protocol Date	November 13, 2018
Study Design	Prospective, single arm, experimental, non-significant risk study.
Inclusion Criteria	1. Possession of the following at time of eligibility screening, ascertained from automatic hardware/software/device pairing check: I. iPhone (5s or later) with iOS version 12.1.1 or later defined as iPhone model/iOS version used to complete screening eligibility. II. Apple Watch (Series 1-4) with watchOS version 5.1.2 or later defined as Apple Watch model/watchOS paired with iPhone used to complete screening eligibility. 2. At least one of the following by self-report before consent: I. Irregular Rhythm Notification II. ECG app classification of Atrial Fibrillation III. ECG app classification of Inconclusive defined as "Inconclusive," "Heart Rate Over 120," or "Heart Rate Under 50" 3. Age ≥ 22 years at time of eligibility screening, ascertained from self-reported date of birth. 4. Current resident of the United States at time of eligibility screening, defined by self-reported state of residence within the 50 states of the United States or District of Columbia, and will reside in the United States for the length of the study. 5. Proficient in written and spoken English, defined by self-report of comfort reading, writing, and speaking English on iPhone. 6. Valid phone number associated with iPhone, ascertained from self-report. 7. Valid email address, ascertained from self-report.

Exclusion Criteria	1. Shared iCloud account 2. Shared AppleWatch

Objectives	1a. To measure the proportion of participants with an Irregular Rhythm Notification (IRN) prior to enrollment who have atrial fibrillation or atrial flutter (AF) confirmed by ambulatory electrocardiographic (ECG) patch monitoring. 1b. To measure the proportion of participants with an ECG app classification of Atrial Fibrillation (ECG app-AFib) prior to enrollment who have AF confirmed by ambulatory ECG patch monitoring. 2a. To measure the proportion of participants who receive an IRN or ECG app-AFib reporting contact with a non-study healthcare provider at 15 and 60 days after study enrollment. 2b. To measure the proportion of participants with an ECG app classification of inconclusive prior to enrollment who have AF confirmed by ambulatory ECG patch monitoring. 2c. To measure the proportion of participants who have AF confirmed by ambulatory ECG patch monitoring by age at enrollment (< 65 and 65+).

Primary Outcome	Atrial fibrillation or atrial flutter of at least 30 seconds duration on an ambulatory ECG patch monitor.
Secondary Outcomes	1. Arrhythmias other than AF on an ambulatory ECG patch monitor 2. Self-reported contact with healthcare provider
Study Devices	Irregular Rhythm Notification feature ECG app
Duration of Study Participation	Enrollment will occur over approximately a 6 month-period. Every participant will complete baseline questionnaires and wear an ambulatory ECG patch for up to 7 days. Every participant will receive an app notification to complete a web-based Patient Reported Outcomes (PRO) survey 15 and 60 days following enrollment. Participation in the study will end after completion of the 60 day PRO survey or after 90 days, whichever date is earlier.
Number of Participants	Approximately 2600 participants will be enrolled

1.1 INTRODUCTION

1.1 Background

Undiagnosed Atrial Fibrillation

Atrial fibrillation and atrial flutter (AF) affect approximately 6 million people in the US, with prevalence expected to rise to 12 million by 2030 (Benjamin 2018). AF is associated with higher rates of stroke, heart failure, thromboembolic events, cognitive decline, and death (Benjamin 2018). However, approximately 13% of AF is estimated to be undiagnosed (Turakhia 2018). There is a need to identify new strategies to identify these individuals to connect them with appropriate treatments to prevent stroke and modify risk factors.

Guidelines for AF Screening

The USPSTF recently published an "I" recommendation for AF screening in asymptomatic individuals, finding that there was insufficient evidence to recommend for or against screening for AF (USPSTF 2018, Jonas 2018). Specifically, there was insufficient evidence on whether screening for asymptomatic AF improves health outcomes compared to usual care. Additionally, potential harms of screening were not well-characterized.

Wearable Health Technology

Wearable health technologies offer a novel approach for disease screening. Users wear devices on a daily basis, and there is an opportunity to screen for AF passively and actively in the moment when an individual has symptoms. This approach may be able to identify more individuals with AF. Virtual care models may be able to connect these individuals with treatment. Additionally, wearable technology may be able to facilitate monitoring of disease and management of risk factors (Chen 2018).

Irregular Rhythm Notification (IRN)

The Irregular Rhythm Notification (IRN) feature is a software-only mobile medical application that is intended to be used with the Apple Watch. The feature analyzes pulse rate data to identify episodes of irregular heart rhythms suggestive of AFib. Using observable variations in PPG signal intensity, changes in blood flow can be measured and beat-to-beat pulse measurements can be made. During normal sinus rhythm, there is minimal variation in pulse. However, during AF, the beat-to-beat variability increases significantly. Therefore, a PPG signal can be used to differentiate between a regular pulse and an irregular pulse that may be indicative of AF.

An algorithm has been developed by Apple to identify periods of irregular pulse based on PPG signal variation as measured by the Irregular Pulse Notification Algorithm (IPNA). The time between PPG signal peaks observed during periods of minimal arm movement are marked as intervals between heart beats. A tachogram is a period of time over which heart beat intervals

are measured. The degree of beat-to-beat variability is measured from spot tachograms over the course of approximately one minute intervals. An irregular tachogram is flagged when the variability, measured using a Poincare plot, crosses a predefined threshold. An IPNA checks multiple tachograms over a period of approximately an hour or more. An IRN is then sent to the user when a period of an irregular pulse suggestive of AFib has been identified. This feature was granted FDA de novo classification on 9/11/2018.

ECG app
The ECG app is a software-only mobile medical application intended for use with the Apple Watch to create, record, store, transfer, and display a single channel ECG similar to a Lead I ECG. The ECG app processes electrical signals from two sensors on the Apple Watch - an electrode on the back of Apple Watch and an electrode on the digital crown. A user opens the ECG app on their Apple Watch, places a finger on the digital crown, and remains still for 30 seconds to capture an ECG. The ECG app analyzes the waveform to determine the presence of atrial fibrillation (AFib) or sinus rhythm on a classifiable waveform. The ECG app waveform is stored in the Health App and can be exported as a .pdf. This app was granted FDA de novo classification on 9/11/2018.

1.2 Study Rationale

The IRN feature and ECG app will be available to the public as a software update in early December 2018. IRN will be available on Apple Watch Series 1-4; ECG app will be available on Apple Watch Series 4.

The data collected in this study will provide an understanding of the experience of participating users of IRN and ECG app to help inform how mobile medical applications, such as the IRN and ECG app may be optimally used to facilitate heart disease screening and treatment. Findings may also help to inform the design of future research to determine whether use of Apple Watch to facilitate novel approaches to heart disease screening and treatment can improve health outcomes.

2.0 STUDY OBJECTIVES

2.1 Research Question

The overall objective is to characterize the ability of Apple Watch rhythm analysis software to identify AF and facilitate subsequent clinical evaluation among users who contact AppleCare.

2.2 Study Objectives

1a. To measure the proportion of participants with an Irregular Rhythm Notification (IRN) prior to enrollment who have atrial fibrillation or atrial flutter (AF) confirmed by ambulatory electrocardiographic (ECG) patch monitoring.

1b. To measure the proportion of participants with an ECG app classification of Atrial Fibrillation (ECG app-AFib) prior to enrollment who have AF confirmed by ambulatory ECG patch monitoring.

2a. To measure the proportion of participants who receive an IRN or ECG app-AFib reporting contact with a non-study healthcare provider at 15 and 60 days after study enrollment.

2b. To measure the proportion of participants with an ECG app classification of inconclusive prior to enrollment who have AF confirmed by ambulatory ECG patch monitoring.

2c. To measure the proportion of participants who have AF confirmed by ambulatory ECG patch monitoring by age at enrollment (< 65 and 65+).

3.0 OUTCOMES

3.1 Primary Outcome

Atrial fibrillation or atrial flutter of at least 30 seconds duration on an ambulatory ECG patch monitor.

3.2 Secondary Outcomes

1. Arrhythmias other than AF on an ambulatory ECG patch monitor
2. Self-reported contact with healthcare provider

4.0 STUDY DESIGN

4.1 Overall Study Design

Scope

This will be a prospective, single arm, experimental non-significant risk study, conducted with the assistance of eligible participants.

Participants calling into AppleCare self-reporting that they have received an IRN or ECG app classification of AF or inconclusive (defined as “Inconclusive,” “Heart Rate Over 120,” or “Heart Rate Under 50”) will be offered information about participation in the study, and the AppleCare representative will offer to e-mail the participants a link to download the Study App for more information. If the participant agrees, the participant will be emailed a link to download the Study App. Once downloaded, the Study App will provide the information about the study and screen for eligibility. If the participant meets the eligibility criteria and wishes to enroll in the study, the Study App will initiate the consenting process and provide the consent and authorization to sign in the app. Participants who install the Apple Heart Study 1.2 App and meet the eligibility criteria proceed to consent and then be enrolled in the study. Participants will be required to provide signed informed consent; once enrolled they will complete a short questionnaire to collect demographic information, medical history, and health status, after which the study period will commence.

Monitoring

After enrollment in the study, participants will be prompted to contact the telemedicine technology services company, American Well Corporation (together with the Online Care Group, the "Study Telehealth Provider") to conduct Study Telehealth Visit #1 (voice or video). During Study Telehealth Visit #1, participants will undergo a virtual medical evaluation which will include an abbreviated assessment for symptoms, medical history, and medications. Participants with urgent symptoms (chest pain, shortness of breath, fainting/losing consciousness) will be directed to an urgent care clinic or emergency room for medical evaluation. For participants with non-urgent symptoms, the Study Telehealth Provider will order an ambulatory ECG monitor (i.e. an ePatch) from BioTelemetry. Participants will be expected to contact the Study Telehealth Provider within 30 days of enrollment. Study participants will be reminded to initiate Study Visit #1 with reminders via email and phone calls if needed. Participants who call after 30 days will still be able to obtain an ePatch and undergo remaining study procedures, but may not be included in all analyses.

The participants will be mailed the ambulatory ECG monitor, which the participant will then be requested to wear for up to 7 days. The minimum analyzable time acceptable for primary

analysis is one hour. Participants with the ECG app will be asked to take an ECG app recording at least 2 times each day while wearing the ePatch, as well as after receiving an irregular rhythm notification. The participant will then mail the ambulatory ECG monitor back to BioTelemetry, which will generate a standard technical report that will be read by BioTelemetry's technical readers. The report will be adjudicated by two board-certified clinicians, and a final report will be made available to the Study Telehealth Provider by BioTelemetry.

A second study visit, Study Visit #2, will occur with the Study Telehealth Provider once the ambulatory ECG monitor results are available. After the final ambulatory ECG monitor report is made available to the Study Telehealth Provider, the Study Telehealth Provider will contact the participant to prompt them to complete Study Visit #2. During Study Visit #2 (voice or video), the ambulatory ECG monitor results will be reviewed. If AF or any other arrhythmias have been detected in reviewing the ambulatory ECG monitor data, or if there are other non-urgent symptoms needing further evaluation, the Study Telehealth Provider will direct the participant to their primary health care provider, or other health care provider as deemed appropriate by the Study Telehealth Provider. The report and visit summary will be made available to the participant and also to participant's physician or health care provider, if the participant provides his/her physician information and permission to send that physician a copy of the report. For participants who do not have an established primary health care provider, the Study Telehealth Provider will encourage and offer advice in establishing a primary care provider per standard Study Telehealth Provider protocol.

Patient Reported Outcomes (PROs)

Fifteen and sixty days after enrollment, participants will receive a separate app notification to complete the patient reported outcomes (PRO) questionnaires. The participant will be notified about the sixty day questionnaire even if the participant does not complete the fifteen day questionnaire. These outcomes will include whether or not the participant contacted a primary health care provider and what additional treatments or diagnostic tests they underwent. They will also be asked questions related to measures of anxiety about testing, experience with the IRN feature and ECG app, and health status. Participants will receive reminders via notifications from the app to complete the PROs prior to the due date (within 30 days of notification).

5.0 STUDY POPULATION

5.1 Inclusion Criteria

1. Possession of the following at time of eligibility screening, ascertained from automatic hardware/software/device pairing check:
    I. iPhone (5s or later) with iOS version 12.1.1 or later defined as iPhone model/iOS version used to complete screening eligibility.
    II. Apple Watch (Series 1-4) with watchOS version 5.1.2 or later defined as Apple Watch model/watchOS paired with iPhone used to complete screening eligibility.
2. At least one of the following by self-report before consent:
    I. Irregular Rhythm Notification
    II. ECG app classification of Atrial Fibrillation
    III. ECG app classification of Inconclusive defined as “Inconclusive,” “Heart Rate Over 120,” or “Heart Rate Under 50”
3. Age ≥ 22 years at time of eligibility screening, ascertained from self-reported date of birth.
4. Current resident of the United States at time of eligibility screening, defined by self-reported state of residence within the 50 states of the United States or District of Columbia, and will reside in the United States for the length of the study.
5. Proficient in written and spoken English, defined by self-report of comfort reading, writing, and speaking English on iPhone.
6. Valid phone number associated with iPhone, ascertained from self-report.
7. Valid email address, ascertained from self-report.

5.2 Exclusion Criteria

1. Shared iCloud account
2. Shared AppleWatch

5.3 Recruitment

Apple Watch Series 1-4 users who telephone AppleCare about the Irregular Rhythm Notifications or ECG app and report having received an IRN or ECG app classification of atrial fibrillation or inconclusive on repeated measurement will be offered information about participation in the study. AppleCare provides technical support for Apple hardware, software, and services. For issues related to the IRN feature and ECG app, participants will be routed via telephone to an AppleCare advisor who is trained in handling technical questions and any medical complaints related to the use of the IRN feature and ECG app. Users who indicate interest in the study will be emailed a link to download and install the Study App. The Study App will determine study eligibility and enroll the participant in the study. If, 60 days after the

study opens, there is evidence that enrollment rates will not be adequate to meet enrollment goals for each subgroup, then alternative recruitment strategies may be employed to help reach recruitment goals.

6.0 STUDY DEVICES

Device 1 Name: Irregular Rhythm Notification feature

The Irregular Rhythm Notification Feature is a software-only, FDA-cleared, mobile medical application that is intended to be used with the Apple Watch. The feature analyzes pulse rate data to identify episodes of irregular heart rhythms suggestive of AFib and provides a notification to the user. The feature is intended for over-the-counter (OTC) use. It is not intended to provide a notification on every episode of irregular rhythm suggestive of AFib and the absence of a notification is not intended to indicate no disease process is present; rather the feature is intended to opportunistically surface a notification of possible AFib when sufficient data are available for analysis. These data are only captured when the user is still. Along with the user's risk factors, the feature can be used to supplement the decision for AFib screening. The feature is not intended to replace traditional methods of diagnosis or treatment.

Device 2 Name: ECG app

The ECG app is a software-only, FDA-cleared, mobile medical application intended for use with the Apple Watch to create, record, store, transfer, and display a single channel electrocardiogram (ECG) similar to a Lead I ECG. The ECG app determines the presence of atrial fibrillation (AFib) or sinus rhythm on a classifiable waveform. The ECG app is not recommended for users with known arrhythmias other than atrial fibrillation.

The ECG app is intended for over-the-counter (OTC) use. The ECG data displayed by the ECG app is intended for informational use only. The user is not intended to interpret or take clinical action based on the device output without consultation of a qualified healthcare professional. The ECG waveform is meant to supplement rhythm classification for the purposes of discriminating AFib from normal sinus rhythm and not intended to replace traditional methods of diagnosis or treatment.

7.0 STUDY PROCEDURES

Time (days)	Event
0	Study Opens
60	Interim check of enrollment
180	End Enrollment
270	Study Closes (latest date for completion of PRO questionnaire)
270+	Analyses

Table 1. Study Timeline

7.1 Eligibility Determination and Enrollment

The potential participant will first download the Apple Heart Study 1.2 App. The app will automatically ensure compatibility with the iPhone iOS version and Watch version. If compatible, the participant will be able to continue forward in the app. An overview of the study will be displayed in the app.

The participant will then advance to a screen for study enrollment, where they will confirm whether they meet general participation requirements. The participant will be asked questions based on study inclusion and exclusion criteria. The app will automatically determine eligibility based on the responses provided. If the participant is determined to be eligible, they will initiate the consenting process with an in-app consent and authorization form to be read and signed if they agree to participate.

Participants will be able to enroll between STUDY START DATE and END OF ENROLLMENT (STUDY START DATE + 6 months).

On END OF ENROLLMENT, enrollment will close. The study period will end on END OF ENROLLMENT + 60.

A 15-day PRO will become available 15 days after enrollment, no later than END OF ENROLLMENT + 15. A 60-day PRO will become available 60 days after enrollment, no later than END OF ENROLLMENT + 60. All PROs will be due by end of study on END OF ENROLLMENT + 90. After this date, all monitoring will end, the Study Telehealth Provider line will be closed and no further data will be collected.

Enrollment may be terminated early if more than 400 participants receiving an IRN and more than 400 participants using the ECG app are diagnosed with AF by ECG patch. Enrollment will be reviewed at STUDY START DATE + 60 days**.** If enrollment in each of the study subgroups outlined in the objectives appears that it will not achieve a sufficient number of subjects to meet study goals, we will enhance recruitment by targeting recruitment strategies to the group(s) of participants at risk for failing to meet study goals or extend the duration of enrollment.

7.2 Enrollment: Consent, Baseline Demographics and Medical History Collection

The Apple Heart Study 1.2 is an app-based research study utilizing the iOS platform. As in other mobile-mediated research studies, the informed consent process in the study is conducted remotely in a completely self-administered setting with no required physical contact with the research team prior to consent and enrollment.

The approach to informed consent for the study has been adapted accordingly to ensure the ethical requirement of informedness, i.e. that participants are adequately informed about the research before participation, is met. Potential candidates as well as enrolled participants will be able to contact a study hotline (available 24/7 at 1-800-358-2286) anytime and have the ability to ask questions and request clarifications at any time prior to or during the study. This hotline will be open from the study start date until study closure.

Participants who successfully pass the eligibility criteria will be directed to a page requesting their consent to participate. Participants will be asked to read and sign the study informed consent and authorization document within the app if they agree and are willing to participate. A copy of the signed study consent and authorization document will be available for review and download to the participant via the app.

After consenting to participate, the participant will be directed to complete a questionnaire to collect self-reported baseline demographics, medical history, and health status.

A participant will be considered enrolled if the participant has consented and completed onboarding questionnaires.

7.3 Procedures for Study Visit #1

7.3.1 Study Telehealth Provider

American Well (Boston, MA) is a healthcare technology company that developed the Telehealth platform being used to support study visits. The American Well technology supports mobile-based interactions between participants and providers during the study, in

which both the participant and provider can see and hear each other through American Well's proprietary videoconferencing capabilities. Virtual visits can be conducted using a wireless or network connection, meaning a study participant can initiate a visit from anywhere in the 50 United States of District of Columbia. American Well's platforms are a SaaS (Software as a Service) offering—this means all operational hardware and support software is housed and maintained within American Well data centers and is serviced by the American Well Hosting Operations department. American Well is a PCI-compliant and is designed to meet HIPAA security requirements, HITRUST-certified, federally recognized security platform.

The Online Care Group (OCG) is American Well's clinical partner. OCG providers are responsible for conducting the study required assessments during study visits. All OCG physicians are licensed, board certified, have 10-15 years of experience in a brick-and-mortar practice, and have undergone a vigorous training on American Well's platform. Additionally, the OCG has an internal credentialing process that meets all standards as dictated by the National Committee for Quality Assurance. The OCG's staff physician-led credentialing committee (comprised of a chief medical officer, staff physician, and director of behavioral health) reviews and approves all practitioners before they are permitted to practice on the American Well System.

Study Telehealth Provider Team, a term used throughout this protocol, relates to physicians from the OCG, Quality, Customer Support (Level 1 agents operating the 24-hour hotline and Level 2), and the Network Operations Center (NOC) staff who will coordinate visits and facilitate the communication of patch report results and clinical summaries to the participant. All these groups provide services through American Well platform.

7.3.2 Study Telehealth Provider Visit #1

The Study App will provide a button for the participant to connect with the Study Telehealth Provider. The first connection with the Study Telehealth Provider will constitute Study Visit #1.

After the participant connects with the Study Telehealth Provider team, they will undergo a study visit. The participant will be asked about cardiovascular clinical signs and symptoms. If the Study Telehealth Provider concludes that the participant has a medical emergency, the Study Telehealth Provider will follow its emergency protocol and either instruct the participant and/or a family member, if available, to call emergency medical services (EMS) or will call on the participant's behalf if the participant and/or a family member are unable to contact EMS. Participants with a medical emergency will not be prescribed an ePatch.

Once emergency symptoms have been ruled out, the telehealth clinician will perform an abbreviated review of medical history and perform a virtual review of physical symptoms. The telehealth provider will also confirm which of the following the participant received: Irregular

Rhythm Notification, ECG app classification of AF, or ECG app classification of inconclusive. If the participant cannot confirm having received any of the above notifications or classifications, the Study Telehealth Provider will not prescribe an ePatch. The information obtained will assure that the Study Telehealth Provider Data Collection variables [see 7.3.3 Study Telehealth Provider Data Collection] are obtained.

The visit summary will be made available to the participant and also to participant's physician or health care provider, if the participant provides the Study Telehealth Provider information of participant's physician and permission to send that physician a copy of the report. Any referral visits will be conducted outside of the study, at the discretion of the participant, and at the cost of the participant.

The Study Telehealth Provider will provide the participant information about the ePatch, answer any questions the participant might have, and contact BioTelemetry to initiate the order and shipment of the ambulatory ECG monitor (ePatch).

7.3.3 Study Telehealth Provider Data Collection – Visit #1

The following data elements will be collected during the study visit:

1. Demographics
2. IRN or ECG app results
3. Past medical history
4. Medications
5. Symptoms
6. Clinical assessment
7. Complaints or adverse events

7.4 Procedures for Ambulatory ECG Patch

7.4.1 BioTelemetry Flow

1. The Study Telehealth Provider will order the ECG patch from BioTelemetry and communicate information necessary for mailing ECG patch and study data management to BioTelemetry.

2. If the participant did not have Study Visit #1 within 30 days of enrollment, participant will still be able to receive a patch monitor and continue with study procedures including PROs, but they will not be included in the primary analyses.

3. BioTelemetry will mail the ambulatory ECG monitor to the participant.

4. The participant will wear the ambulatory ECG monitor for up to 7 days and mail the monitor back to BioTelemetry.

5. After the ambulatory ECG monitor has been worn by the participant for up to 7 days and returned back to BioTelemetry, BioTelemetry will perform data extraction and an initial technical read of the ambulatory ECG findings by trained ECG technicians. The ECG technician review will determine if the participant has any serious or potentially life-threatening abnormality. Although rare, this includes atrial fibrillation with sustained rapid ventricular rates, sustained ventricular tachycardia or ventricular fibrillation, high-degree heart block, and long pauses. If one of these urgent arrhythmias is identified, then the participant will be contacted and directed to local emergency care or advised how to seek local emergency care. Best attempt will be made to send the ECG report to participant's emergency care provider. After confirmation that a participant's ambulatory ECG data does not have any of these urgent arrhythmias, the ambulatory ECG study will be processed into the adjudication workflow. The adjudication workflow is described in a separate charter.

6. The adjudication process will result in generation of a final adjudicated report.

7. Once the adjudicated report is complete, it will be issued to the Study Telehealth Provider.

7.4.2 Procedures for ECG patch wear

The BioTelemetry ePatch Monitor will be used for ambulatory ECG monitoring. The battery life with a single channel recording is 7 days. The participant will be instructed to wear the ePatch for up to 7 days. However, the data collected from a participant will be considered adequate for a participant with a minimum analyzable time of 1 hour.

BioTelemetry will send participants, via courier, an ambulatory ECG monitoring kit containing one sensor and two adhesive patches. If the adhesive patch is no longer functional, the sensor

can be moved to the backup adhesive patch. At the end of the recording period, the participant will be required to mail the monitor back to BioTelemetry using the supplied prepaid mailer.

In the event it is discovered that the participant never received the ePatch due to a shipping error or became lost in transit, then BioTelemetry will issue a second ePatch to that participant. Any subsequent loss of ePatches will not be replaced.

Approximately 14-20 days after enrollment it is expected that most participants will have completed wearing the patch for up to 7 days and will have returned the patch to BioTelemetry via a provided tracked USPS mailer. The ambulatory ECG monitor should be received by BioTelemetry within 45 days from enrollment. Those who return patches beyond 45 days after enrollment or do not begin wearing their patch within 14 days of patch shipment will be included in the fall-out subgroup, however they will still be eligible for a follow-up visit with the Study Telehealth Provider. Those who never return the ambulatory ECG monitor will also be placed in the fall-out subgroup.

7.5 Procedures for Apple Watch wear

Participants will be asked to wear their Apple Watch as they would with normal use. Participants with a Series 4 Apple Watch will be asked to take an ECG at least 2 times each day while wearing the ECG patch. In addition, participants will be asked to take an ECG app recording after receiving each irregular rhythm notification.

7.6 Procedures for Study Visit #2

Once the ePatch has been received by BioTelemetry and the final report has been adjudicated, BioTelemetry will issue a notification to the Study Telehealth Provider. The participant will be notified by way of a secure email that their patch report is ready and will be instructed to contact the Study Telehealth Provider for Study Visit #2 through a button in the app. It is expected that this visit will occur between 15-45 days after enrollment, depending on timing of ambulatory ECG monitor wear, mailing, and interpretation.

The Study Telehealth Provider will review the ambulatory ECG monitoring report with the participant and make any necessary recommendations to the participant. The Study Telehealth Provider will then refer participants with AF, any clinically relevant cardiac arrhythmias, or any non-urgent symptoms requiring follow up detected on patch monitoring to their primary health care provider for further treatment and diagnostic testing. For participants without established primary health care providers, the Study Telehealth Provider will offer referral per standard Study Telehealth Provider protocols. The ambulatory ECG monitoring report and visit summary will be made available to the participant and also to participant's physician or health care provider, if the participant provides the Study Telehealth Provider information of participant's physician and permission to send that physician a copy of the report. Any referral

visits will be conducted outside of the study, at the discretion of the participant, and at the cost of the participant.

Symptoms, disposition recommendations, and any adverse events reported will be logged.

7.7 Study Telehealth Provider Additional Visits

Participants may contact the Study Telehealth Provider through a button in the app outside of the scheduled study visits if they have symptoms concerning for arrhythmia that they wish to discuss with a provider, or questions/concerns about the study. The Study Telehealth Provider will review the participant's symptoms and refer participants to emergency medical services or their primary health care provider. Visits, symptoms, and any adverse events reported will be logged.

7.8 PRO Instruments at 15 and 60 days

Participants will be notified by the app to complete the 15 and 60-day PRO questionnaires at 15 and 60 days following enrollment. The questionnaires will be administered through a web-based survey, and the participant will have 30 days, up until END OF ENROLLMENT + 90, to complete them. Participants will receive reminders via notifications from the app to complete the PRO questionnaires. Questions will ask if the participant followed up with the Study Telehealth Provider and/or a non-study health care provider, received an AF diagnosis, was evaluated in-person by a non-study health care provider, the type of non-study health care provider and/or specialists, received additional cardiac testing, received other clinical arrhythmia diagnoses, anxiety as a result of participation, health status, and experience with the IRN feature and ECG app.

7.9 Data to be collected from HealthKit and Apple Watch

There will be two phases to HealthKit and Apple Watch data collection. Phase 1 will occur between the study start date and approximately January 2019. Phase 2 will occur from approximately January 2019 and later. Participants in each phase will consent to the specific data to be collected in each phase. If a participant begins participation in Phase 1 of the study and remains in the study when Phase 2 begins, the participant will be re-consented for Phase 2.

In Phase 1 of the study, no data will be collected from HealthKit or Apple Watch. In Phase 2 of the study, this study will collect participant data from the Apple Watch and iPhone, including heart rate tachograms, IRNs, and ECG app results. Data will include ECG waveform data from the ECG app. Data will be prospectively collected, beginning after consent and continuing until the end of study. In addition, we will retrospectively collect IRNs and ECG app classifications that were recorded within the 14 days prior to consent.

7.10 Time and Events Schedule

Evaluation	Screening and Eligibility	Consent and Enrollment	Study Visit #1	Study Visit #2	15- Day PRO	60-Day PRO
Inclusion/ Exclusion Criteria	**X**					
Informed Consent		**X**				
Demographics/ Medical History Questionnaire		**X**				
Health status		**X**				**X**
Experience with IRN feature and Apple Watch ECG app					**X**	
Ambulatory ECG Monitor – Introduction/Shipment			**X**			

Virtual Review of Medical History / Physical Symptoms			X			
Ambulatory ECG Monitor - Results Review				**X**		
Arrhythmia Recommendations for PCP referral				**X**		
Survey Completion					**X**	**X**

7.11 Participant Recontact

For participants who do not complete study procedures on time, study staff may contact the participant by email or phone to encourage timely completion of study procedures.

7.12 Participants that may be excluded from specific analyses

Participants may be excluded from some analyses for incomplete data or for various other reasons. The reasons may include:

1. Failure to contact Study Telehealth Provider within 30 days of enrollment.
2. Failure to be deemed eligible for ePatch wear due to emergent symptoms, determined at Study Visit #1.
3. Failure to return an ePatch within 45 days of enrollment.
4. Failure to begin wearing ePatch within 14 days of patch shipment
5. Failure to verify at Study Visit #1 that the participant had a cohort classification as either (1) Irregular Rhythm Notification, or status of (2) Afib or (3) Inconclusive via the ECG app (i.e., with at least 1 ECG recorded within the 14 days before study enrollment indicating classification of either AFib or Inconclusive, where the latter is defined as "Inconclusive," "Heart Rate Over 120," or "Heart Rate Under 50")
6. Withdrawal from the study per Section 9.0

8.0 ADVERSE EVENTS REPORTING

All suspected adverse events (AEs) will be reported to the Study Safety Monitoring Desk at the Stanford Center for Clinical Research (SCCR) by the Study Telehealth Provider Team. The Study Safety Monitoring Desk will review all suspected AEs and determine relatedness to the device (related to the IRN feature, Apple Watch ECG app, or ePatch) and seriousness.

8.1 Definitions and Classification

Term	Definition	Reference
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the device.	ISO 14155-1
Serious Adverse Event (SAE)	Adverse event that a) Led to death, b) Led to serious deterioration in the health of the participant, that either resulted in 1) A life-threatening illness or injury, or 2) A permanent impairment of a body structure or a body function, or 3) In-patient or prolonged hospitalization, or 4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) Led to fetal distress, fetal death or a congenital abnormality or birth defect	ISO 14155-1

8.2 Adverse Events (AEs)

The Study Safety Monitoring Desk is responsible for determining whether the adverse event occurred and is related to the IRN feature, ECG app on Apple Watch, ePatch, or associated with participation in the study.

Possible AEs include the following:

- Skin rash due to wearing the ambulatory ECG monitor (ePatch);
- Skin itchiness due to wearing the ambulatory ECG monitor (ePatch);
- Blister due to wearing the ambulatory ECG monitor (ePatch);
- Skin rash on wrist due to wearing the Apple Watch;
- Pressure artifacts on wrist due to wearing the Apple Watch;
- Signs or symptoms related to use of the IRN feature or ECG app on Apple Watch. The common signs and symptoms include stress and anxiety and associated symptoms that may include dizziness, depression, palpitations, tremors, sleep difficulty, and shortness of breath.

The following occurrences are not to be regarded as AEs:

- Underlying (pre-existing) symptoms or diseases, unless there is an increase in severity or frequency during the course of the investigation;
- Receipt of an IRN;
- Detection of atrial fibrillation or other irregular heartbeat through the IRN feature or ECG App;
- Detection of atrial fibrillation or other irregular heartbeat through ePatch;
- Pre-planned procedure(s);
- Complaint about iPhone or Apple Watch functionality;
- Failure of the participant to regularly wear the Apple Watch or to wear the ePatch
- Apple Heart Study 1.2 app, IRN feature, ECG app, and ePatch functionality issues that do not allege an adverse event

8.3 Serious Adverse Event

If an event is determined by the Study Safety Monitoring Desk to be related to the IRN feature, ECG app, or ePatch, the Study Safety Monitoring Desk will further investigate the event for classification as a Serious Adverse Event.

8.4 Reporting of Suspected Device-Related Serious Adverse Event

8.4.1 Related to IRN feature or Apple Watch ECG App

Possible adverse events related to the IRN feature or ECG app will be reported to the sponsor within 2 business days of being reviewed by the Study Safety Monitoring Desk. The Study Safety Monitoring Desk will conduct further investigation of these events and determine seriousness. The investigation of these events will be completed and reported to the sponsor within 20 days of initial report to sponsor.

8.4.2 Related to ePatch

Events confirmed to be Serious Adverse Events and related to the ePatch will be reported to the BioTelemetry by the Study Safety Monitoring Desk.

8.5 Reporting of Adverse Events (AEs) to IRB

Adverse events will be promptly reported to the IRB if they meet the definition of an Unanticipated Problem (UP), as defined in section 12.1. Timeframes for UP reports are as follows:

1. Within 10 working days from when the Stanford study team learns of the event
2. Within 5 working days from when the Stanford study team learns of the event for unexpected deaths or life-threatening experiences related to the research.

9.0 WITHDRAWAL

Every participant should be encouraged to remain in the study until they have completed the protocol-required follow-up period. If the participant withdraws prematurely from the study, the reason for withdrawal should be documented. Possible reasons for premature withdrawal may include, but are not limited to the following:

- Withdrawal of consent: participant decides to withdraw from the study for any reason. This may be concluded if/when a participant taps the withdraw button within the app or asks to be withdrawn.
- Investigators believe it is in the best interest of the participant to discontinue the study, for any reason.
- It is discovered that participant does not meet inclusion/exclusion criteria

Withdrawal Process:

Participants will have the option to withdraw from the study by tapping a "Withdraw from Study" button within the app. This will disable notifications and will result in a cessation of data collection. If a participant calls the Study Telehealth Provider requesting withdrawal from the study, the Study Telehealth Provider will instruct the participant how to initiate withdrawal on the app. It will not be possible for any party other than the study participant themselves to withdraw from the study. In the few cases where the participant has initiated contact with the Study Telehealth Provider, and thereafter selects "Withdraw from Study" on the app, they may still receive follow-up communication from the Study Telehealth Provider. In order to stop further communication, these participants would need to inform the Study Telehealth Provider Team that they wish to be withdrawn.

Once withdrawn, participants would be able to re-enroll only by reinstalling the application, but will be considered a new study participant without linkage to their prior data.

The following will be considered lost-to-follow-up:

- Death of the participant
- Lost/stolen iPhone and/or Apple Watch

10.0 STATISTICAL CONSIDERATIONS

10.1 Analysis Sets

All analyses will be reported for the overall cohort, as well as by cohort status determined at enrollment: (1) Irregular Rhythm Notification, and status of (2) Afib or (3) Inconclusive via the ECG app (i.e., with at least 1 ECG recorded within the 14 days before study enrollment indicating classification of either AFib or Inconclusive, where the latter is defined as "Inconclusive," "Heart Rate Over 120," or "Heart Rate Under 50".

The Full Analysis Set (FAS) will consist of all enrolled participants who complete the informed consent process. This analysis set will be used to summarize subject demographics, medical history, adverse events, self-reported health status, diagnosis, and contact with the health care provider.

The ePatch eligible analysis set (EEAS) will consist of those in the FAS deemed eligible to receive an ePatch at Study Visit #1.

The ePatch Analysis Set (EAS) will consist of all those in the EEAS who receive and return an ePatch with at least 1 hour of usable data and who do not belong to the Fallout Group.

The Fallout Subgroup Analysis Set (FOG) will consist of participants meeting the criteria of Section 7.10. Demographic and medical history information will be presented for this analysis set.

Objectives 1a, 1b, and 2b and 2c will be conducted using the EAS, whereas Objective 2a will be conducted using the EEAS. The analyses for Objectives 1a, 1b, and 2b and 2c will be repeated in the EEAS as a sensitivity analysis using appropriate methods for handling missing data.

10.2 Outcomes and Definitions

10.2.1 Primary Outcome

Atrial fibrillation or atrial flutter of at least 30 seconds duration on an ambulatory ECG patch monitor for a participant who received an IRN or Apple Watch ECG app-AFib classification prior to enrollment.

10.2.2 Secondary Outcomes

1. Arrhythmias other than AF on an ambulatory ECG patch monitor
2. Self-reported contact with a non-study healthcare provider

10.3 Statistical Approaches to Outcome Analyses

There are no pre-specified statistical hypotheses in this clinical study. Descriptive statistics and 95% confidence intervals will be presented using available data as detailed below.

10.3.1 Primary Outcome Analyses

Objective 1a Analysis

This proportion will be estimated as the ratio of the number of participants in the EAS who have atrial fibrillation or atrial flutter of at least 30 seconds duration on patch wear and received an IRN before enrollment, divided by the number of participants in the EAS who received an IRN before enrollment. An exact 95% two-sided confidence interval will also be presented. We will also describe the number of participants who received an IRN before or during ECG enrollment with arrhythmias other than atrial fibrillation.

Objective 1b Analysis.

This proportion will be estimated as the ratio of the number of participants in the EAS who have atrial fibrillation or atrial flutter of at least 30 seconds duration on patch wear and received an ECG app-AFib classification before enrollment divided by the number of participants in the EAS who received an ECG app-AFib classification before enrollment. An exact 95% two-sided confidence interval will also be presented. We will also describe the number of participants who received an ECG app-Fib before enrollment with arrhythmias other than atrial fibrillation.

10.3.2 Secondary Outcome Analyses

Objective 2a Analysis

This proportion will be estimated as the ratio of the number of participants who received an IRN or ECG app-AFib in the EEAS who reported contact with a non-study healthcare provider at 15 (and separately at 60) days after study enrollment divided by the number of participants in the EEAS who received an IRN or ECG app-AFib. An exact 95% two-sided confidence interval will also be presented.

Objective 2b Analysis

This proportion will be estimated as the ratio of the number of participants in the EAS who have atrial fibrillation or atrial flutter of at least 30 seconds duration on patch wear and received an ECG app-Inconclusive status before enrollment, divided by the number of participants in the EAS who received an ECG app-Inconclusive status before enrollment. An exact 95% two-sided confidence interval will also be presented. We will also describe the

number of participants who received an ECG app-Inconclusive status before enrollment with arrhythmias other than atrial fibrillation.

Objective 2c Analysis.

This proportion will be estimated as the ratio of the number of participants who have atrial fibrillation or atrial flutter of at least 30 seconds duration on patch wear who are greater than 65 years of age at enrollment divided by the number of participants enrolled who are greater than 65 years of age at enrollment using the EAS. An exact 95% two-sided confidence interval will also be presented. We will also describe the number of participants who are 65 years of age or older at enrollment with arrhythmias other than atrial fibrillation.

A similar proportion will be presented for those less than 65 years of age at enrollment.

10.3.3 Subgroup Analyses

The proportions and 95% confidence intervals for the primary outcomes (study objectives 1a and 1b) will be performed separately by age group (<55, 55-64, ≥65), sex, and race/ethnicity, cohort status determined at enrollment, and cohort status determined throughout the observations period (e.g., received an IRN during patch wear, received an ECG app-Inconclusive classification during patch wear). Chi-squared tests will be performed to determine if these proportions differ significantly by subgroup.

10.3.4 Additional Analyses

Subject accountability, baseline demographics and medical history, survey results, and adverse events will be summarized using descriptive statistics for the FAS. Baseline demographics and medical history will also be summarized for participants in the FOG. Additional details may be found in the SAP.

Additional analyses may be performed to gain further insight into the relationships between receiving notifications or app-based classifications and ePatch data. Importantly, we will additionally evaluate use of the IRN feature and behavioral response to notifications as captured in the 15 day PRO. Similarly, we will evaluate behavioral response to engaging a healthcare provider as captured in the 60 day PRO among those in the FAS by relevant participant characteristics.

Apple may perform additional analyses using participant data to support future product development.

10.4 Handling of Missing Data

Participants who do not respond to the 15 or 60 day PROs, do not have at least an hour of analyzable wear time from the ambulatory ECG monitor or do not return a patch within 45 days will be considered to have missing data. Methods for missing data such as multiple imputations will be implemented when performing analyses on the FAS or the EEAS. The assumptions of the missing data method will be evaluated in sensitivity analyses.

10.5 Sample Size and Power Considerations

This clinical study is not designed to test any pre-specified statistical hypotheses. Because all participants enrolling in this clinical trial will either have received an irregular rhythm notification (IRN) or an ECG app-AFib classification, this sample size justification applies to Objectives 1a and 1b. To address our aims, we require 400 IRN participants that are exclusively in the IRN group (i.e., who do not enter the study via the ECG app), who are deemed eligible for ePatch receipt and who return their ePatches, and 400 participants who exclusively enroll via the ECG-app classification of AFib, who are deemed eligible for ePatch receipt and who return their ePatches. This sample size provides sufficient precision for our purposes, yielding a 95% confidence interval with a width that is no greater than 0.10 when addressing the primary objectives. Further, it does not require assessment or unblinding of ePatch results on an ongoing basis. If, after enrolling 500 participants, we observe that there is 50% overlap or greater between participants who enroll through both the IRN and the ECG app, we will modify our targeted enrollment with the understanding that the reporting of findings will be accompanied with a detailed context of the types of subjects that contribute to both the point estimates of interest. Given these considerations, a targeted enrollment of 2600 participants is suggested. This allows for approximately a 35% attrition rate and a 50% overlap between participant types (IRN vs ECG-app).

10.6 Limitations

Because the study population is enriched for participants with irregular rhythms and inconclusive results who call AppleCare in response to receiving an IRN, an ECG classification of Atrial Fibrillation, or an ECG classification of Inconclusive, the results of this study may not be generalizable to the broader population of Apple Watch users.

11.1 TRAINING

To ensure accurate, complete, and reliable data, the Stanford study team in conjunction with sponsor, will provide instructional material to Study Telehealth Provider, BioTelemetry, ECG Adjudicating Clinicians and other study personnel as appropriate.

12.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with applicable FDA regulations (21 CFR Parts 11, 50, 54, 56, 803, and 820, as applicable).

12.1 Institutional Review Board

The protocol must be submitted to the appropriate Institutional Review Board (IRB) and written approval must be obtained prior to enrolling any participants. Yearly approvals for the continuation of the study must be obtained by the Investigator.

In addition to the IRB reports submitted during the yearly approval process, certain events require prompt reporting to the IRB. The timeline and type of events will follow the most updated policy of the governing IRB, but in general, those events, as relevant to this protocol, include:

1. Unanticipated Problems Involving Risks to Participants or Others (UPs): Events (internal or external, deaths, life-threatening experiences, injuries, or other) occurring during the research study, which meet all of the following criteria:
    a. Unexpected in terms of nature, severity, or frequency; and
    b. Related to participation in the research or there is a reasonable possibility or likelihood that the event may have been caused by the procedures involved in the research; and
    c. Harmful – places research participants or others at a greater risk of harm than was previously known or recognized.
2. New Information that indicates a change to the risks or potential benefit of the research in terms or severity or frequency or impacts the participant's willingness to participate.
3. Noncompliance with the IRB approved protocol and other applicable policies when the event is:
    a. Possibly serious (affects the rights and welfare of participants)
    b. Possibly continuing (a pattern of noncompliance that continues to occur)
4. Complaint that is unresolved by the research team
5. Other events or information

12.2 Informed Consent and HIPAA Authorization

The Informed Consent will be provided within the study app and will employ ResearchKit electronic consent framework for the signature view to obtain signed and dated informed consent and HIPAA authorization prior to enrollment. Signed consent forms will be stored on an encrypted server which is 21 CFR Part 11 compliant. The protocol and informed consent form must be approved by the reviewing IRB prior to commencement of the study. Any subsequent revisions to the informed consent form must also receive IRB approval prior to use.

12.3 Confidentiality of Participants

Participant confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique participant identification code (ID number) will be used that allows identification of all data reported for each participant. The ID number will be randomly generated.

Participant information collected in this study will comply with the applicable standards for protection of privacy of individually identifiable health information. The Sponsor, investigators and all study affiliates will make every reasonable effort to protect the confidentiality of the participants participating in this study. Participant records may be released to governing regulatory authorities, if requested. In all cases, caution will be exercised to assure the data are treated confidentially and that the participant's privacy is protected.

13.0 HUMAN SUBJECTS PROTECTION

13.1 Research participant Selection and Justification of Exclusions

There will be no exclusion from participation in the study on the basis of ethnicity or race. Participants younger than 22 years of age will be excluded from the study, as the target population is adults ≥ 22 years. Participants who are not proficient in written English will be excluded as this will prohibit informed consent as well as completion of any necessary data collection forms. Participants with shared iCloud accounts or Apple Watches will be excluded due to inability to confirm participant-level measures and outcomes.

13.2 Compensation to participants

There will be no direct monetary remuneration to study participants.

14.0 RECORD KEEPING/REPORTING

14.1 Data Collection

The study will create 21 CFR Part 11 compliant data flows for relevant study sources to 21 CFR Part 11 compliant servers housing information on participant demographics, baseline health history, questionnaires, data from the Irregular Rhythm Notification features and ECG app, ambulatory ECG monitor results, Adverse Events, and 15- and 60-day PROs.

14.2 Study Documentation

Study documentation includes but is not limited to all consent forms, app screens, app based forms, Irregular Rhythm Notification data, ECG app data, PROs, ambulatory ECG monitor reports, and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approval, approved and signed participant consent forms, Statement of Investigator form, etc.). The investigator will prepare and maintain complete and accurate study documentation in compliance with applicable federal, state, and local laws, rules, and regulations.

15.0 REFERENCES

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Statistical Analysis Plan

Study Official Title: Evaluation of the use of Apple Watch features for identification of cardiac arrythmias

ClinicalTrials.gov Identifier: NCT03769207

Document Date: December 3 2018

Stanford MEDICINE | Quantitative Sciences Unit

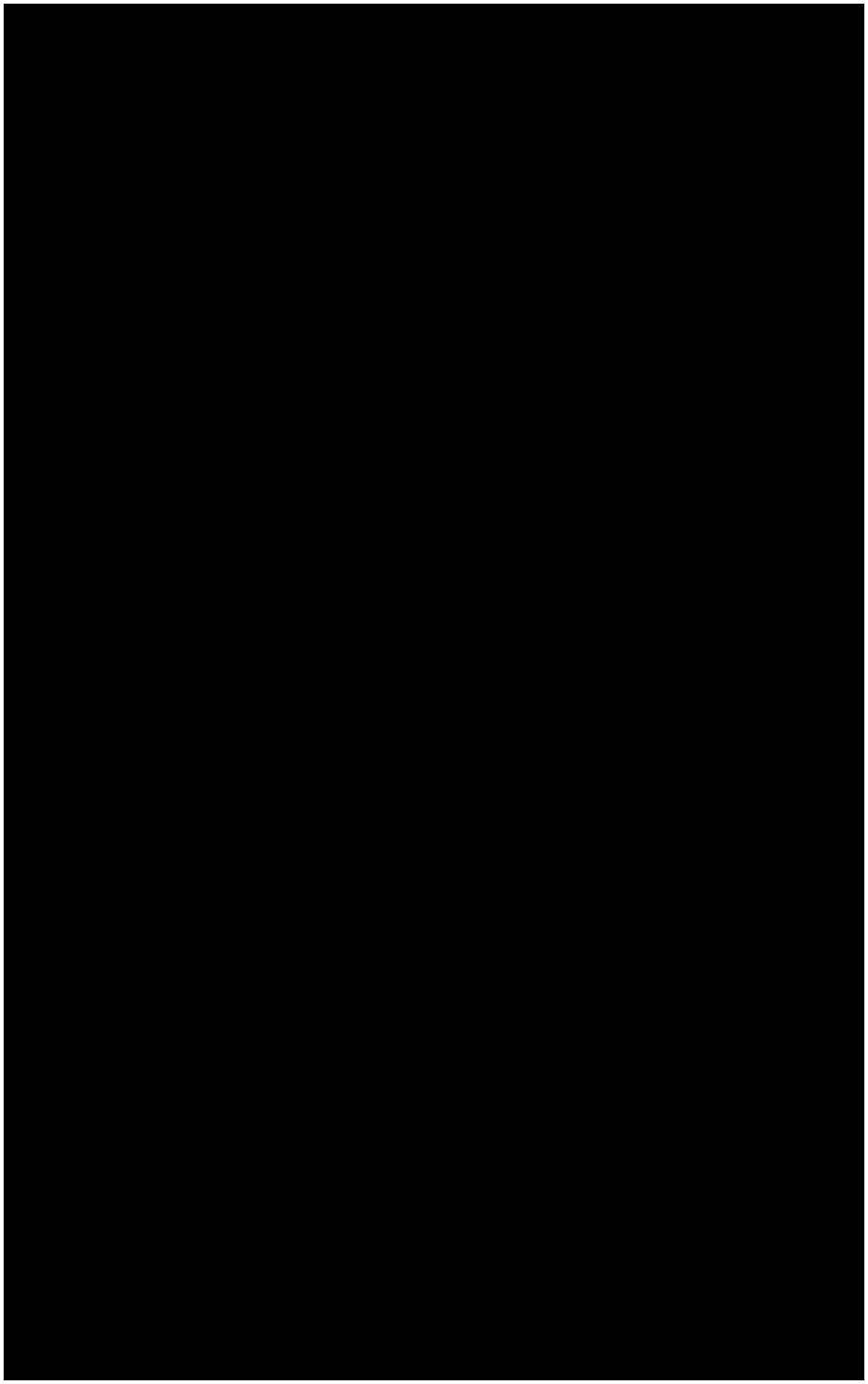
Statistical Analysis Plan

Study Name	Apple Heart Study 1.2
Version Number	1.0
Date	3 December 2018

Apple Heart Study 1.2

Evaluation of the use of Apple Watch features for identification of cardiac arrhythmias

SIGNATURE PAGE



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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this Statistical Analysis Plan (SAP).

Abbreviation or special term	Explanation
AE	Adverse Event
AF	Atrial Fibrillation and Atrial Flutter
AFib	Atrial Fibrillation
Apple Watch ECG app-AFib	Apple Watch ECG app classification of atrial fibrillation
CI	Confidence Interval
EAS	ePatch Analysis Set
EEAS	ePatch Eligibility Analysis Set
ECG	Electrocardiography, Electrocardiogram, Electrocardiographic
FAS	Full Analysis Set
FOG	Fallout Subgroup
IRN	Irregular Rhythm Notification
IPNA	Irregular Pulse Watch Notification Algorithm
PAC	Premature Atrial Contractions
PPG	Photoplethysmography, Photoplethysmogram
PRO	Patient Reported Outcome
PVC	Premature Ventricular Contractions
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SV1	Study Visit 1
SV2	Study Visit 2

Revision history

Revision	Date	Section/Page	Changes Made -- Reasons for the Change

INTRODUCTION

This statistical analysis plan (SAP) is a comprehensive and detailed description of the strategy, rationale and statistical techniques that we will use to evaluate the ability of the Apple Watch Irregular Pulse Watch Notification Algorithm (IPNA) feature and Electrocardiography (ECG) app to identify atrial fibrillation or atrial flutter (AF) and facilitate subsequent clinical evaluation among users who contact AppleCare.

1. STUDY DETAILS

1.1 Study objectives

Objective 1a: To measure the proportion of participants with an Irregular Rhythm Notification (IRN) prior to enrollment who have atrial fibrillation or atrial flutter (AF) confirmed by ambulatory electrocardiographic (ECG) patch monitoring.

Objective 1b: To measure the proportion of participants with an ECG app classification of Atrial Fibrillation (ECG app-AFib) prior to enrollment who have AF confirmed by ambulatory ECG patch monitoring.

Objective 2a: To measure the proportion of participants who receive an IRN or ECG app-AFib reporting contact with a non-study healthcare provider at 15 and 60 days after study enrollment.

Objective 2b: To measure the proportion of participants with an ECG app classification of inconclusive prior to enrollment who have AF confirmed by ambulatory ECG patch monitoring.

Objective 2c: To measure the proportion of participants who have AF confirmed by ambulatory ECG patch monitoring by age at enrollment (< 65 and 65+).

1.2 Study design

This will be a prospective, single arm, experimental, non-significant risk study conducted with the assistance of eligible participants wearing an Apple Watch Series 1-4 with the IRN feature or an Apple Watch Series 4 with the ECG app who receive an IRN or an ECG app classification of AF or “inconclusive”.

The Irregular Rhythm Notification (IRN) feature is a software-only mobile medical application that analyzes pulse rate data to identify episodes of irregular heart rhythms suggestive of AFib. Using observable variations in photoplethysmogram (PPG) signal intensity, changes in blood flow can be measured and beat-to-beat pulse measurements can be made. During normal sinus rhythm, there is minimal variation in pulse. However, during AF, the beat-to-beat variability increases significantly. Therefore, a PPG signal can be used to differentiate between a regular pulse and an irregular pulse that may be indicative of AF.

An algorithm has been developed by Apple to identify periods of irregular pulse based on PPG signal variation as measured by the Irregular Pulse Notification Algorithm (IPNA). The time between PPG signal peaks observed during periods of minimal arm movement are marked as intervals between heart beats. A tachogram is a period of time over which heart beat intervals are measured. The degree of beat-to-beat variability is measured from spot tachograms over the course of approximately one minute intervals. An irregular tachogram is flagged when the variability, measured using a Poincare plot, crosses a predefined threshold. An IPNA checks multiple tachograms over a period of approximately an hour or more. An IRN is then sent to the user when a period of an irregular pulse suggestive of AFib has been identified.

The ECG app is a software-only mobile medical application intended for use with the Apple Watch to create, record, store, transfer, and display a single channel ECG similar to a Lead I ECG. The ECG app processes electrical signals from two sensors on the Apple Watch - an electrode on the back of Apple Watch and an electrode on the digital crown. A user opens the ECG app on their Apple Watch, places a finger on the digital crown, and remains still for 30 seconds to capture an ECG. The ECG app analyzes the waveform to determine the presence of atrial fibrillation (AF) or sinus rhythm on a classifiable waveform. The ECG app waveform is stored in the Health App and can be exported as a .pdf. The ECG app provides rhythm classifications such as AF, “Inconclusive”, “Heart Rate Over 120”, or “Heart Rate Under 50”. The ECG app group classifications; “Inconclusive”, “Heart Rate Over 120”, or “Heart Rate Under 50” are all considered inconclusive for the purposes of this study and are considered eligible for this study. Both the IRN feature and the ECG app were granted United States Food and Drug Administration (FDA) de novo classification on 9/11/2018.

Participants who call into AppleCare and self-report having received an IRN or ECG app classification of AF or inconclusive will be offered information about participation in the study. The AppleCare representative will offer to e-mail the participant a link to download the Study App for more information. If the participant agrees, the participant will be emailed a link to download the Study App. Once downloaded, the Study App will provide the information about the study and screen for eligibility. If the participant meets the eligibility criteria and wishes to enroll in the study, the Study App will initiate the consenting process and provide the consent and authorization to sign in the app. Participants who install the Apple Heart Study 1.2 App and meet the eligibility criteria proceed to consent and then enroll in the study. Participants will be required to provide signed informed consent; once enrolled they will complete a short questionnaire to collect demographic information, medical history, and health status, after which the study period will commence.

After enrollment, participants will be prompted to contact the Study Telehealth Provider to conduct Study Visit #1 (SV1) via voice or video. During SV1, participants will undergo a virtual medical evaluation which will include an abbreviated assessment for symptoms, medical history, and medications. Participants with urgent symptoms (chest pain, shortness of breath, fainting/losing consciousness) will be directed to an urgent care clinic or emergency room for medical evaluation. For participants with non-urgent symptoms, the Study Telehealth Provider will order an ambulatory ECG monitor (i.e., an ePatch) from

BioTelemetry. Participants will be expected to contact the Study Telehealth Provider within 30 days of enrollment. Study participants will receive reminders via email and phone calls if needed to initiate SV1. Participants who call after 30 days will still be able to obtain an ePatch and undergo remaining study procedures, but may not be included in all analyses.

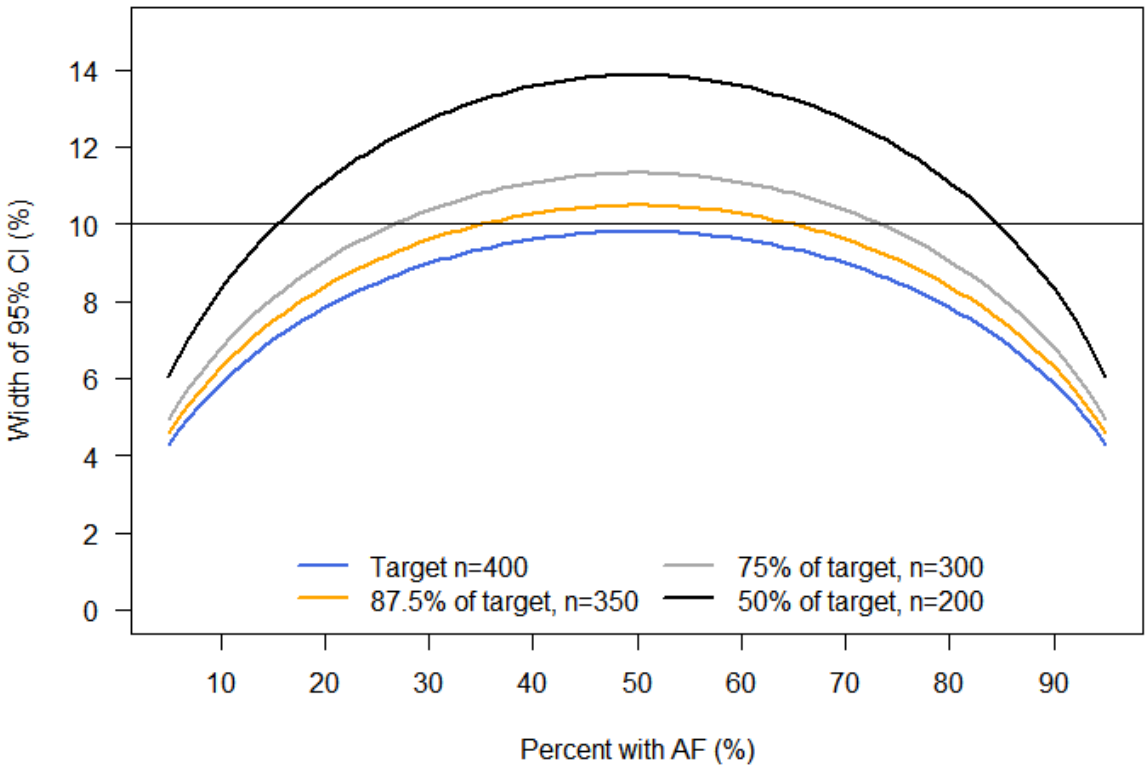
Participants will be mailed the ePatch, and once received, the participant will be required to wear it for up to 7 days. The minimum analyzable time acceptable for primary analysis is one hour. Participants with the ECG app will be asked to take an ECG app recording at least twice daily while wearing the ePatch, as well as after receiving an irregular rhythm notification. The participant will then mail the ambulatory ECG monitor back to BioTelemetry within 45 days of enrollment, which will generate a standard technical report that will be read by BioTelemetry's technical readers. The report will be adjudicated by two board-certified clinicians, and a final report will be made available to the Study Telehealth Provider by BioTelemetry.

After the final ambulatory ECG monitor report is made available to the Study Telehealth Provider, the Study Telehealth Provider will contact the participant to prompt them to complete Study Visit #2 (SV2). During SV2 the ePatch results will be reviewed. If AF or any other arrhythmias have been detected in reviewing the ambulatory ECG monitor data, or if there are other non-urgent symptoms needing further evaluation, the Study Telehealth Provider will direct the participant to their primary health care provider, or other health care provider as deemed appropriate. The report and visit summary will be made available to the participant and also to the participant's physician or health care provider, if the participant provides his/her physician information and permission to send that physician a copy of the report. For participants who do not have an established primary health care provider, the Study Telehealth Provider will encourage and offer advice in establishing a primary care provider per standard Study Telehealth Provider protocol.

1.3 Number of Participants Needed to Address Objectives

This clinical study is not designed to test any pre-specified statistical hypotheses. Because all participants enrolling in this clinical trial will either have received an IRN or an ECG app-AFib classification, we derived the number of enrolled participants needed to achieve our desired precision for addressing Objectives 1a and 1b.

To obtain a 95% confidence interval (CI) with a width no greater than 0.10 when addressing Objective 1a we will require 400 IRN participants that are exclusively in the IRN group (i.e., who do not enter the study via the ECG app), who are deemed eligible for ePatch receipt and who return their ePatches. Similarly, for Objective 1b to obtain a 95% CI with a width no greater than 0.10 we will require 400 participants who exclusively enroll via the ECG-app classification of AFib, who are deemed eligible for ePatch receipt and who return their ePatches.



The figure above displays the 95% CI width for the target sample size of 400 (over the range of possible AF percents we could observe) and three sample sizes that represent a failure to meet the target; n=350 (87.5% of target), n=300 (75% of target) and n=200 (50% of target). The height of the lines (the vertical axis) correspond to the CI width. The horizontal axis corresponds to the percent AF observed. As noted 400 patches (the blue line) will ensure the estimated CIs are no wider than 10%. The lines representing a failure to meet the target number of returned ePatches for each group shows at worst the CI could be as wide as 13.9% at 50% of the target and a percent with AF of 50%. However, even at 87.5% or even 75% of the recruitment target the worst case is a CI width of 11.3% and in both cases a modest amount of possible AF percentages will yield a CI with a width < 10%.

If, after enrolling 500 participants, we observe that there is 50% overlap or greater between participants who enroll through both the IRN and the ECG app, we will modify our targeted enrollment with the understanding that the reporting of findings will be accompanied with a detailed context of the types of subjects that contribute to both estimates addressing Objectives 1a and 1b.

Allowing for an approximate attrition rate of 35% and an overlap of 50% between participant types (IRN vs ECG-app) we calculated a minimum target enrollment of 2600 participants.

Further, the expected period for completion of study recruitment is approximately 6 months. If, 60 days after the study opens, there is evidence that enrollment rates will not be adequate to meet enrollment goals for each subgroup, then alternative recruitment strategies will be employed to help reach recruitment goals.

2. ENDPOINTS

2.1 Primary Endpoints

The primary endpoint of the study is

- An indicator for whether atrial fibrillation or atrial flutter of at least 30 seconds duration on an ambulatory ECG patch monitor.

2.2 Secondary Endpoints

The secondary endpoints are

- Arrhythmias other than AF on an ambulatory ECG patch monitor.
- Self-reported contact with healthcare provider.

3. ANALYSIS SETS

The Full Analysis Set (FAS) will consist of all enrolled participants who complete the informed consent process. This analysis set will be used to summarize subject demographics, medical history, adverse events, self-reported health status, diagnosis, and contact with the health care provider.

The ePatch Eligibility Analysis Set (EEAS) will consist of those in the FAS deemed eligible to receive an ePatch at Study Visit #1. This analysis set will be used to assess Objective 2a.

The ePatch Analysis Set (EAS) will consist of all those in the EEAS who receive and return an ePatch with at least 1 hour of usable data and who do not belong to the Fallout Subgroup. This analysis set will be used to assess Objectives 1a, 1b, and 2b and 2c. We will repeat these analyses in the EEAS as a sensitivity analysis using appropriate methods for handling missing data.

The Fallout Subgroup Analysis Set (FOG) will consist of participants who enroll and complete the informed consent process but otherwise do not complete the study. Reasons for study incompletion include; failure to contact Study Telehealth Provider within 30 days of enrollment, being deemed ineligible at Study Visit #1 for ePatch wear due to emergent symptoms, ePatch not returned within 45 days of enrollment, failure to start wearing ePatch within 14 days of shipment, unable to verify at Study Visit #1 a study eligible IRN or ECG-app notification, study withdrawal (i.e., withdrawal of consent), or lost to follow-up (i.e., death). We will present demographic and medical history information for this analysis set.

4. ANALYSIS METHODS

4.1 General Principles

Method for Constructing Confidence Intervals

We will construct confidence intervals using the asymptotic Gaussian approximation. For proportions near 1 or 0, a potential drawback of this method is confidence intervals containing values outside of the range [0,1]. If we encounter confidence intervals with bounds outside of the [0,1] range we will instead construct the confidence intervals using the bias corrected and accelerated (BCa) method of creating a bootstrap confidence interval.

Incomplete Dates

If only the year of a date is given (YY), then the date shall be set to 'YY0701'. If only the year and month of a date is given (YYMM), then the date shall be set to 'YYMM15'.

Descriptive Statistics

Numerical variables will be summarized using standard summary statistics including the number of participants, mean, standard deviation, median, 10^{th} and 90^{th} percentile and range (i.e., minimum and maximum) as appropriate. For categorical data, proportions will be presented in a frequency table format.

Multiple Patches per Participant

In rare instances where a single user ID is associated with data available from more than one patch, only data from the final patch will be used in statistical analyses.

4.2 Study Population

Participant Disposition

The number and percent of participants who completed the study, discontinued from the study, and reasons for discontinuation from the study will be summarized by age group, participant classification (i.e., IRN, ECG App classification of AFib, or ECG App classification of inconclusive) and overall, for the FAS (table shown by age for illustrative purposes).

Age group, yrs	Measures	IRN	ECG: AFib	ECG: inconclusive
< 55	N Completed the study, n (%) Discontinued from study, n (%) Reasons for discontinuation			

55-64	N Completed the study, n (%) Discontinued from study, n (%) Reasons for discontinuation			
65+	N Completed the study, n (%) Discontinued from study, n (%) Reasons for discontinuation			
Overall	N Completed the study, n (%) Discontinued from study, n (%) Reasons for discontinuation			

Participants having protocol deviations will be summarized using the FAS population.

Age group, yrs	**FAS, N**	**Protocol deviations, n (n/N)**
<55		
55-64		
65+		
Overall		

Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized overall, by age, and by participant classification using the EEAS and EAS. No statistical tests will be performed for comparison of any baseline measurement by age group.

All summaries of continuous characteristics will be based on non-missing observations and the percent of participants missing values will be reported. For categorical characteristics, percents will be calculated out of the total number of participants in the data set (i.e., each denominator includes the number of participants with missing/unknown values for the variable), where the percentage missing will also be reported.

Table 2 Summaries of Demographic and Other Characteristics at Baseline.

Characteristic	Summarized as	Categories
Age	Categorical and Continuous	<55, 55-64, 65+ years
Gender	Categorical	Female Male Non-binary
Race/Ethnicity	Categorical	American Indian or Alaska Native Asian Black or African American Hispanic, Latino or Spanish origin Middle Eastern or North African Native Hawaiian or Other Pacific Islander White Some other race, ethnicity or origin Prefer not to respond
BMI	Categorical and Continuous	<30 kg/m2 and ≥30 kg/m2
Average number of cigarettes smoked per day	Categorical	None 1-10 11-20 21-40 41 or more Rather not say
Average number of alcoholic beverages consumed per week	Categorical	Less than 1 1-5 6-9 10 or more Rather not say

Medical History	Categorical	High blood pressure or hypertension Diabetes mellitus Heart attack or myocardial infarction Heart failure Stroke or transient ischemic attack Peripheral arterial disease Ever diagnosed you with atrial fibrillation or atrial flutter
Told by doctor had a type of irregular heart beat	Categorical	Atrial Tachycardia Frequent Premature Ventricular Contractions (PVCs) Frequent Premature Atrial Contractions (PACs) Supraventricular Tachycardia (SVT) Ventricular Tachycardia (VT) None of the above I don't know
Currently taking medications	Categorical	Aspirin Warfarin (coumadin) Apixaban (Eliquis) Dabigatran (Pradaxa) Edoxaban (Savaysa) Rivaroxaban (Xarelto) None of these
Notification received	Categorical	Irregular rhythm notification ECG app on Apple Watch result of "Atrial Fibrillation" ECG app on Apple Watch result of "Inconclusive" ECG app on Apple Watch result of "Heart Rate over 120" ECG app on Apple Watch result of "Heart Rate under 50" I'm not sure
How would you rate your physical health	Categorical	Excellent Very good Good Fair Poor

To what extent are you able to carry out your everyday physical activities	Categorical	Completely Mostly Moderately A little Not at all
How would you rate your mental health	Categorical	Excellent Very good Good Fair Poor
How would you rate your satisfaction with your social activities and relationships	Categorical	Excellent Very good Good Fair Poor

Medications at study visits 1 and 2

Medications reported during study visit 1 and 2 will be summarized using the EEAS group by drug category or generic drug name by age group and overall. We will also describe new medications started between SV1 and enrollment and SV2 and SV1.

Drug Category or Name	**N Responding SV1 (%)**	**N on Medication SV1 (%)***	**N Responding SV2 (%)**	**N on Medication SV2 (%)***
Beta blockers				
Calcium channel blockers				
Aspirin				
Anticoagulants				

* Percent calculated as percent of participants who responded to whether they used the corresponding drug type.

4.3 Analysis Methods

Analysis of the Primary Endpoint Addressing Objective 1a and 1b

For Objectives 1a and 1b we have designed the study to estimate the proportion of participants diagnosed with AF within a 0.10 confidence interval width.

Objective 1a – The proportion of participants with an IRN prior to enrollment who have AF confirmed by ambulatory ECG patch monitoring.

This proportion will be estimated as the ratio of the number of participants in the EAS who have atrial fibrillation or atrial flutter of at least 30 seconds duration on patch wear and received an IRN before enrollment, divided by the number of participants in the EAS who received an IRN before enrollment. An exact 95% two-sided confidence interval will also be presented. We will also describe the number of participants who received an IRN before or during enrollment with arrhythmias other than atrial fibrillation.

Objective 1b Analysis – The proportion of participants with an ECG app-AFib classification prior to enrollment who have AF confirmed by ambulatory ECG patch monitoring.

This proportion will be estimated as the ratio of the number of participants in the EAS who have atrial fibrillation or atrial flutter of at least 30 seconds duration on patch wear and received an ECG app-AFib classification before enrollment divided by the number of participants in the EAS who received an ECG app-AFib classification before enrollment. An exact 95% two-sided confidence interval will also be presented. We will also describe the number of participants who received an ECG app-Fib before enrollment with arrhythmias other than atrial fibrillation.

Analysis of the Secondary Endpoints Addressing Objectives 2a, 2b and 2c

Objective 2a Analysis - The proportion of participants with an IRN or ECG app-AFib classification reporting contact with a non-study healthcare provider at 15 and 60 days after study enrollment.

This proportion will be estimated as the ratio of the number of participants who received an IRN or ECG app-AFib classification in the EEAS who reported contact with a non-study healthcare provider at 15 (and separately at 60) days after study enrollment divided by the number of participants in the EEAS who received an IRN or ECG app-AFib. An exact 95% two-sided confidence interval will also be presented.

Objective 2b Analysis

This proportion will be estimated as the ratio of the number of participants in the EAS who have atrial fibrillation or atrial flutter of at least 30 seconds duration on patch wear and received an ECG app-Inconclusive status before enrollment, divided by the number of participants in the EAS who received an ECG app-Inconclusive status before enrollment. An exact 95% two-sided confidence interval will also be presented. We will also describe the

number of participants who received an ECG app-Inconclusive status before enrollment with arrhythmias other than atrial fibrillation.

Objective 2c Analysis

This proportion will be estimated as the ratio of the number of participants who have atrial fibrillation or atrial flutter of at least 30 seconds duration on patch wear who are greater than 65 years of age at enrollment divided by the number of participants enrolled who are greater than 65 years of age at enrollment using the EAS. An exact 95% two-sided confidence interval will also be presented. We will also describe the number of participants who are 65 years of age or older at enrollment with arrhythmias other than atrial fibrillation. A similar proportion will be presented for those less than 65 years of age at enrollment.

Sensitivity and Sub-analyses

The proportions and 95% confidence intervals for Objectives 1a and 1b will be performed separately by age group (<55, 55-64, ≥65), sex, race/ethnicity, cohort status determined at enrollment, cohort status determined during patch wear (e.g., received an IRN during patch wear, received an ECG app-Inconclusive classification during patch wear) and selected medical history conditions (e.g., ever diagnosed you with atrial fibrillation or atrial flutter, or ever had a stroke, Transient Ischemic Attack (TIA) or "Mini Stroke"). Chi-squared tests will be performed to determine if proportions differ significantly by subgroup.

Baseline demographics and medical history, survey results, and adverse events will be summarized using descriptive statistics for the FAS. Baseline demographics and medical history will also be summarized for participants in the FOG.

Additional analyses may be performed to gain further insight into the relationships between receiving notifications or app-based classifications and ePatch data. Importantly, we will additionally evaluate use of the IRN and ECG app features and behavioral response to notifications as captured in the 15 day PRO. Similarly, we will evaluate behavioral response to engaging a healthcare provider as captured in the 60 day PRO by relevant participant characteristics.

To understand the sensitivity of our findings for study objectives utilizing the EAS that requires at least 1 hour of useable data from participants in the EEAS, we will vary the requirement that participants with less than 1 hour of wear time be considered as missing their ECG data. We will also conduct additional sensitivity analyses considering the following alternative minimum wear times: 6 hours, 1 day, 2 days, and 5 days.

Adverse Events

A participant will be counted once for a reported AE even if the participant had multiple occurrences of that AE. We will summarize the proportion of participants reporting anxiety and rash in the EEAS and EAS. All AEs will be collected; however, these AEs are of most interest to the study device (anxiety) and are highest risk in the study (rash).

Adverse Events	**N EEAS**	**% EEAS**	**N EAS**	**% EAS**
Anxiety				
Rash				

The participant incidence of all serious adverse events will be presented for each analysis set by age group and overall.

Age group, yrs	**N SAEs**	**N unique participants with SAEs**	**SAEs/participants with SAEs**
< 55			
55-64			
65+			
Overall			

Analysis of Fall-Out Subgroup

The FOG (a subset of the FAS) will include participants who are enrolled but otherwise do not complete the study. Possible reasons are listed in Section 3. We will describe baseline characteristics for this group and for those in the FOG that have completed the PRO, we will report rates of contact with a non-study healthcare provider.

4.5 Definitions

Irregular Arrhythmias

AF is defined as irregular QRS complexes with no clearly discernible p-waves lasting 30s or more ever during the ECG monitoring. In tertiary analyses, we consider definitions requiring longer periods of AF, up to 24 hours.

Sinus arrhythmia is defined as a beat-to-beat variation lasting at least 120ms with discernible sinus p-waves ever during the ECG monitoring.

Frequent PACs are defined as p-waves that are observed before the predicted time interval. A participant is considered to have frequent PACs if they average 30 or more PACs/hour during the ambulatory ECG monitoring.

Frequent PVCs are defined as wide QRS complexes without preceding p-waves. A participant is considered to have frequent PVCs if their (total number of PVCs/total number of beats)*100% is ≥ 5% and very frequent PVCs if ≥ 15% during the ambulatory ECG monitoring. (See the next subsection for criteria used to indicate presence of PACs and PVCs at the tachogram-level.)

Intermittent heart block is defined as the presence of p-waves that are not followed by a QRS complex and are not preceded by a gradually prolonging PR interval. No minimum amount of time is required.

Multifocal atrial tachycardia is defined as an irregular, narrow complex tachycardia with discernable preceding p-waves preceding the QRS complex that are of at least two different morphologies, lasting at least 30 seconds.

Atrial tachycardia with variable conduction is defined as an irregular narrow complex tachycardia with one predominant p-wave morphology lasting at least 30 seconds. The p-waves are followed by QRS complexes with varying ratios, from one QRS for every p-wave, to one QRS for multiple p-waves. The p-waves are a distinct morphology from typical flutter waves.

Notification Concordance

The ambulatory ECG monitoring will be considered to be concordant with either an IRN or ECG app-AFib classification before enrollment if 30 seconds of AF is observed on the ambulatory ECG monitor during the period of wear in the study for study participants with at least 1 hour of usable ECG monitor data.

4.6 Handling of Missing Data

Participants who do not respond to the 15 or 60 day PROs, do not have at least an hour of analyzable wear time from the ambulatory ECG monitor or do not return a patch within 45 days will be considered to have missing data. We will use methods for missing data such as multiple imputation when performing analyses on the FAS or the EEAS. We will further evaluate the assumptions of missing data methods in sensitivity analyses.

4.7 Potential Limitations and Mitigation Strategies

We have identified several potential limitations in our planned analyses and have planned various sensitivity analyses and alternate approaches to understand and mitigate the impact of these limitations on our findings. The ePatch is not worn at the time of the initial notification and we may not detect AF on the subsequent ambulatory ECG monitoring, particularly in participants with low burden AF. We additionally expect that some participants will wear their ePatch for a period shorter than 7 days. We acknowledge that several factors may contribute to an overestimated or underestimated proportion of AF in participants who receive an IRN or ECG app-AFib classification. We describe above sensitivity analyses to evaluate the sensitivity of estimates to the minimum wear time for inclusion in the analysis (described in Section 4.3).

In particular, we anticipate several biases that may impact the estimates for Objectives 1a, 1b, 2b and 2c.

- Patch Wear Bias: We anticipate that not all participants will wear their patches for the full 7 day wear period. We acknowledge that wear periods shorter than 7 days and a study design where the ePatch is worn during a period that follows the initial notification (and not simultaneously) will likely contribute to an underestimated true proportion of AF in participants who receive an IRN or ECG app-AFib classification because the AF that triggered the initial notification may not be detected during the subsequent ambulatory ECG monitoring. We will evaluate the sensitivity of our estimates addressing Objectives 1a, 1b, 2b and 2c to the minimum wear time for inclusion in the analysis (described in Section 4.3).

- Missing Data Bias: For some participants, the IRN or ECG app-AFib classification will occur but no subsequent analyzable ECG monitoring data will be available (e.g., participant requires urgent care, participant doesn't return patch). Because these participants will not provide ambulatory ECG monitoring data, they will not be included in analyses to estimate the proportions in Objectives 1a, 1b, 2b and 2c. Their exclusion may bias the estimates up or down. Participants who require urgent care are presumably more likely to have AF and their exclusion would lead to an underestimate. On the other hand, participants who do not return patch may be less sick and their exclusion would result in an overestimate of the proportion of participants with AF. This bias is an inherent limitation of an observational study.

- Observation Period Bias: It is possible that participants may receive an IRN or ECG app-AFib classification but the subsequent ECG monitoring may not be of sufficient length to observe AF.

- Classification self-report bias: For the primary analysis patients will be analyzed according to their self-reported classification status at enrollment. However, a change in data collection in Phase II of the study will allow tachogram data prior to patient enrollment to be used to validate the patient self-reported classification. Sub-group analysis will be performed using Phase II data where classifications will be validated

according to tachogram data and results compared between those who are in agreement with those who are not.

5. INTERIM CHECKS

Interim checks in this study will be performed to assess study recruitment.

Throughout the course of the study, we will check the number of recruited participants according to their cohort designation at enrollment (i.e, IRN, ECG app-AFib classification and ECG app-inconclusive classification). Specifically, at 60 days after the study opens, if enrollment rates are not adequate to meet enrollment goals for each subgroup for the EAS group (i.e. viable ePatch data for assessing the primary study objectives), then alternative recruitment strategies may be employed to help reach recruitment goals. Additionally, recruitment rates will be assessed by age (<65, 65+ years).

	N EAS at 60 days	**Expected N EAS at end of study**	**Meeting study recruitment goals?**
IRN			
ECG app-AFib classification			