Protocol

Study Official Title: Apple Heart Study: Assessment of Wristwatch-Based Photoplethysmography to Identify Cardiac Arrhythmias

ClinicalTrials.gov Identifier: NCT03335800

Document Date: 20 Mar 2018

Protocol

Apple Heart Study

Assessment of Wristwatch-Based Photoplethysmography to Identify Cardiac Arrhythmias

Protocol Version: 8.0

Protocol Date: March 20, 2018

Sponsor: Apple Inc.
1 Infinite Loop
Cupertino CA 95014
United States

Coordinating Principal Investigators and Study Contacts:

Marco V. Perez, MD Assistant Professor of Medicine Stanford University 300 Pasteur Dr., M/C 5773 Stanford, CA 94305 Tel (650) 723-9363 Fax (650) 725-7568 E-mail: mvperez@stanford.edu	Minang (Mintu) Turakhia, MD, MAS Associate Professor of Medicine Stanford University 1070 Arastradero Rd Palo Alto, CA 94304 Phone: (650) 497-9345 E-mail: mintu@stanford.edu

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: Assessment of Wristwatch-Based Photoplethysmography to Identify Cardiac Arrhythmias

Protocol Version: 8.0

Protocol Date: March 20, 2018

This Non-Significant Risk (NSR) study will be conducted in the United States, in accordance with applicable parts of 21 CFR Parts 50, 54, 56 and 812.

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

[redacted]

INVESTIGATORS' SIGNATURE PAGE

STUDY TITLE: Apple Heart Study: Assessment of Wristwatch-Based Photoplethysmography to Identify Cardiac Arrhythmias

Protocol Version: 8.0

Protocol Date: March 20, 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, 56 and 812, and all governing IRB requirements.

TABLE OF CONTENTS

ACRONYMS

AF - Atrial Fibrillation or Atrial Flutter
AHS - Apple Heart Study
CFR - Code of Federal Regulations
DSMB - Data and Safety Monitoring Board
EAS - ECG Analysis Set
ECG - Electrocardiography, Electrocardiogram, Electrocardiographic
EMS - Emergency Medical Services
EOS PRO - End Of Study PRO
FAS - Full Analysis Set
FDA - Food and Drug Administration
HIPAA - Health Insurance Portability and Accountability Act
HITRUST - Health Information Trust Alliance
HR - Heart Rate
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
SC - Steering Committee

PROTOCOL SYNOPSIS

Study Title	Apple Heart Study: Assessment of Wristwatch-Based Photoplethysmography to Identify Cardiac Arrhythmias
Protocol Version	8.0
Protocol Date	March 20, 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 11.0 or later defined as iPhone model/iOS version used to complete screening eligibility. II. Apple Watch (Series 1 or later) with watchOS version 4.0 or later defined as Apple Watch model/watchOS paired with iPhone used to complete screening eligibility. 2. Age ≥ 22 years at time of eligibility screening, ascertained from self-reported date of birth. 3. 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. 4. Proficient in written and spoken English, defined by self-report of comfort reading, writing, and speaking English on iPhone. 5. Valid phone number associated with iPhone, ascertained from self-report. 6. Valid email address, ascertained from self-report.
Exclusion Criteria	1. Self-reported diagnosis of Atrial Fibrillation at the time of consent. 2. Self-reported diagnosis of Atrial Flutter at the time of consent. 3. Currently on anticoagulation therapy, as self-reported at the time of consent.

Study Objectives	Objective 1a: To measure the proportion of participants aged ≥ 65 with irregular pulse watch notifications who have demonstrable atrial fibrillation or flutter (AF) as confirmed by ambulatory electrocardiographic (ECG) patch monitoring. Objective 1b: To measure the proportion of all participants with irregular pulse watch notifications who have demonstrable atrial fibrillation or flutter (AF) as confirmed by ambulatory ECG patch monitoring. Objective 2: To characterize the concordance between pulse irregularity determined using spot tachograms (approximately one minute of beat-to-beat intervals) and AF detected by simultaneous ambulatory ECG patch monitoring. Objective 3: To estimate the rate of initial contact with a health care provider within 3 months after an irregular pulse watch notification.
Co-Primary Endpoints	1. AF of greater than 30 seconds duration detected on ambulatory ECG monitoring for a participant who received an irregular pulse watch notification. 2. Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with AF during time intervals when the spot tachogram is positive for an irregular pulse among those who received a notification.
Secondary Endpoints	1. Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with AF when the Irregular Pulse Notification Algorithm (IPNA) based on multiple tachograms is positive for an irregular pulse among those who received a notification. 2. Self-reported contact with a health care provider within 3 months following an irregular pulse watch notification.
Test Device	Apple Heart Study app

Duration of Study Participation	Participants will have approximately 10 month-period to enroll. For each participant, the monitoring period will begin upon consent for that participant and end on September 1, 2018 (for those who never receive a notification) or on January 31, 2019 (for those who receive a notification). Every participant who receives a notification will receive an in-app Patient Reported Outcomes (PRO) survey within the app 90 days following the notification. All participants will receive a web-based End Of Study PRO (EOS PRO) survey that they will have until January 31, 2019, to complete.
Number of Participants	We anticipate total enrollment to be approximately 500,000 participants. Ambulatory ECG monitoring is expected on approximately 500-5000 participants comprised of participants from two main subgroups (< 65 yrs, ≥ 65 yrs).

1.0 INTRODUCTION

1.1 Background

Impact of Undiagnosed Atrial Fibrillation

Atrial fibrillation, the most common sustained cardiac arrhythmia with an estimated lifetime risk of one in four,[1,2] accounts for 15% of the 700,000 strokes per year in the United States.[3] The prevalence of AF in the United States is estimated to be between 3 and 5 million[4] and this number is expected to rise sharply due to an aging population and a rising age-adjusted incidence of AF. Oral anticoagulation (OAC) has been shown to substantially reduce the risk of AF associated stroke.[5] However, 18% of AF-related strokes occur in patients with asymptomatic or subclinical AF that is newly-detected at the time of stroke.[6] Asymptomatic and subclinical AF have been associated with similar morbidity and mortality rates as symptomatic AF,[7] and with similar rates of silent embolic events.[8] Moreover, untreated AF substantially increases the risk of the development of heart failure and other cardiac complications. Therefore, earlier detection of asymptomatic or subclinical AF could reduce the total public-health burden of ischemic stroke, heart failure, and other AF-related sequelae with upstream therapies.

With an aging population in which AF prevalence is forecast to increase substantially,[1] effective AF screening strategies may have important public health implications.

Guidelines for AF Screening

Contemporary international guidelines on primary prevention of AF-related stroke, and general guidelines on AF management, recommend opportunistic pulse detection (pulse palpation by trained health care personnel during routine health care contact) in patients ≥ 65 years of age.[9,10] Guideline statements recognize the demonstrated improvements to sensitivity for AF detection achieved through ambulatory ECG (both intermittent and continuous) monitoring. Professional society clinical guidelines and the U.S. Preventive Services Task Force have not yet recommended systematic screening for AF in general or high-risk populations.

However, further studies are needed to clarify the effectiveness of screening (e.g., sensitivity/specificity, cost-effectiveness, subsequent health care utilization, and downstream impact on stroke incidence), before endorsing broader AF screening approaches utilizing contemporary technologies.

Prevalence of Undiagnosed AF

Prior work indicates a high rate of undiagnosed AF in the general population. In a back calculating modeling study based on incidence of AF shortly following ischemic stroke in Medicare and commercial claims beneficiaries, there are an estimated 500,000 persons with undiagnosed AF in the United States, with an estimated incremental cost burden of $3.2 billion.[11]

In a study of patients with no AF by history, AF was identified in 10 of 767 (1.3%) participants on baseline electrocardiogram (ECG). Intermittent ECG monitoring over a 2-week period (Zenicor ECG, Zenicor Medical Systems, Stockholm, Sweden), identified an additional 20 of 403 (5.0%) participants with previously undiagnosed AF.[7] Similarly, the SEARCH-AF study screened 1,000 patients with a 30-second single vector ECG rhythm strip coupled to a smartphone device (AliveCor Kardia Mobile, AliveCor, Inc., Ashmore, Australia).[12] In this population (mean age 76 years; 44% male), newly-identified AF was found in 1.5% of participants. Recently, results have been published from the STROKE-STOP study, a large randomized control trial of systematic AF screening of individuals in Sweden who were 75 to 76 years of age.[13] Patients were advised to assess their heart rhythm twice a day or during symptoms such as palpitations, with a handheld heart rate monitor (Zenicor ECG, Zenicor Medical Systems, Stockholm, Sweden). In the 14,487 patients enrolled, 12.3% were found to have AF, 3.0% were found to have previously unknown AF, and 5.1% of the screened population had AF and were not receiving adequate stroke prevention therapy. Screening resulted in the initiation of OAC in 3.7% of the screened population, demonstrating that screening can lead to AF treatment both in patients with newly-diagnosed as well as prevalent AF.

However, given the paroxysmal and asymptomatic nature of AF, brief intermittent screening strategies are highly insensitive and likely to only capture patients with high AF burdens. This issue is highlighted by a recent retrospective study that showed in patients diagnosed with AF after stroke, using a 14-day ambulatory ECG monitor, the median AF burden was 0.33 hours.[14] Similarly, the investigation of prolonged ambulatory ECG screening (30 days) for AF after stroke, as compared to conventional 24-hour Holter monitors, detected 5-fold more AF (16.1% vs. 3.2%).[15] With improvements in AF detection algorithms, long-term implantable loop recorders are being increasingly used to screen for occult AF. However, the benefits of long-term screening with this modality come with the downsides of an invasive procedure.

Wearable Health Technologies

Recently, there has been substantial uptake, both from consumers and patients**,** of wearable health technology such as wrist-worn devices incorporating multiple sensors. Such

technologies can generate large amounts of real-time data on patient activity and heart rate variability, often through photoplethysmography (PPG) based measurements of capillary blood volume. As technologies advance and adoption increases, wearable health technologies will be able to deliver increasingly more complex information on patient health. To date, efficient utilization of these data sources to effect improvement in traditional patient outcomes has been limited. For decades, cardiac implanted electronic devices (e.g., pacemakers and implantable cardioverter defibrillators) have collected and transmitted real time patient data, ranging from measures of patient activity to life-threatening arrhythmia notifications. These systems have been shown to improve clinical outcomes (e.g., time to clinical decision and mortality) and serve as proof of concept for wearable health technology based patient monitoring. However, further investment and study is needed to develop and define wearable health technologies' health care applications.

App Based Health Care Research

Traditional approaches to prospective health care investigation are limited by high start-up costs and large infrastructure requirements. Utilization of apps in health care research can streamline patient consent, data collection, and distribution of health care interventions (e.g., medical information, medication reminders, etc.). App-based research also enables enrollment of a broader population. ResearchKit, an open source framework to conduct medical research, developed by Apple, has been effectively used to operationalize large prospective observational studies. MyHeart Counts, a Stanford led app-based investigation of cardiovascular health and patient activity, demonstrated impressive enrollment metrics, with 50,000 participants enrolled within the first year of launch. Altogether, app based health care research can decrease the barriers to, and costs of, performing large studies quickly.

Apple Watch Irregular Pulse Notification Algorithm (IPNA)

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. A notification is then sent to the user when a period of an irregular pulse consistent with AF has been identified.

1.2 Study Rationale

Leveraging existing wearable technology paired with a novel app-based health algorithm that analyzes heart rate irregularity consistent with AF has the potential to scale opportunistic AF screening strategies across large populations.

In recent years, wearable technology has rapidly diffused into consumer markets and provides unique opportunities to engage individuals on health issues of personal interest, and to collect personal health data. One example of such technology are PPG sensors that can measure heart rate and heart rate variability for exercise and training purposes. However, utilization of this data source to improve patient outcomes has not been fully realized in the health care field. An app-based heart irregularity algorithm that identifies possible AF from collected PPG data and then notifies the user of such potential irregularities could lead to widespread screening and subsequent early AF detection and oral anticoagulation initiation, ultimately resulting in reductions in stroke incidence.

2.0 STUDY OBJECTIVES

2.1 Research Question

The overarching objective is to evaluate the ability of the IPNA to identify AF and guide subsequent clinical evaluation.

2.2 Study Objectives

Objective 1a: To measure the proportion of participants aged ≥ 65 with irregular pulse watch notifications who have demonstrable AF as confirmed by ambulatory ECG patch monitoring.

Objective 1b: To measure the proportion of all participants with irregular pulse watch notifications who have demonstrable AF as confirmed by ambulatory ECG patch monitoring.

Objective 2: To characterize the concordance between pulse irregularity determined using spot tachograms and AF detected by simultaneous ambulatory ECG patch monitoring.

Objective 3: To estimate the rate of initial contact with a health care provider within 3 months after an irregular pulse watch notification.

3.0 ENDPOINTS

3.1 Co-Primary Endpoints

1. Atrial fibrillation or atrial flutter (AF) of greater than 30 seconds duration detected on ambulatory ECG monitoring for a participant who received an irregular pulse watch notification.

2. Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with AF during time intervals when the spot tachogram is positive for an irregular pulse among those who received a notification. This endpoint will be evaluated during time intervals when the watch provides tachogram data. Thus, each participant contributes multiple observations for this endpoint.

3.2 Secondary Endpoints

1. Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with AF when the IPNA based on multiple tachograms is positive for an irregular pulse among those who received a notification.

2. Self-reported contact with a health care provider within 3 months following an irregular pulse watch notification.

3.3 Tertiary Endpoints

1. Arrhythmias, other than AF, detected on an ambulatory ECG monitor that can also result in an irregular pulse. These include sinus arrhythmia, frequent premature atrial contractions, frequent premature ventricular contractions, intermittent heart block, multifocal atrial tachycardia, and atrial tachycardia with variable conduction.

2. AF of greater than 6 minutes, 1 hour, 6 hours, and 24 hours duration detected on an ambulatory ECG monitor following an irregular pulse watch notification.

3. Self-reported initiation of therapies for AF, including anticoagulant, rate-controlling and antiarrhythmic therapy.

4. Self-reported electrical or chemical cardioversion by a health care 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 without a known history of atrial fibrillation or atrial flutter.

Participants who download the Apple Heart Study app and meet the eligibility criteria will enroll on a metered basis, whereby a maximum number of participants will be allowed to enroll, and then proceed to consent. Enrollment will initially be weighted heavily towards participants who are at least 65 years of age. Those who are not enrolled immediately will be placed in a "waiting period", and notified via a notification in the Apple Heart Study app when their opportunity to enroll is available. Participants will be required to provide signed informed consent; once enrolled they will complete a short questionnaire to collect demographic information and medical history, after which the monitoring period will commence.

Monitoring

During the monitoring period, upon the detection of a series of irregular tachograms, and based on the IPNA, the Apple Heart Study app will notify the participant that an irregular rhythm was identified. When notified of a pulse irregularity, participants will be asked to contact the telemedicine technology services company, American Well Corporation (together with Online Care Group, the "Study Telehealth Provider") administered within the app that will manage the participant's study follow-up throughout study participation. Following the first notification, the participant will be reminded daily to contact the Study Telehealth Provider via the app. This reminder will be repeated each day until the participant contacts the Study Telehealth Provider, for a maximum period of 14 days. The first contact made by the participant to the Study Telehealth Provider will constitute Study Visit #1. After 14 days from the initial notification, no further reminders will be sent by the app. The participant will become part of the fall-out subgroup if they do not contact the Study Telehealth Provider and complete Study Visit #1 within 30 days of receiving the first notification. These participants in the fall-out subgroup who call after 30 days will still be able to initiate Visit #1 with the Study Telehealth Provider and undergo remaining study procedures.

During Study Visit #1 (voice/video), participants will undergo a virtual medical evaluation including an assessment for symptoms, medical history, and medication use. 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. Such participants who are directed to either emergency care or urgent care will also be included in the fall-out subgroup.

Participants without urgent symptoms who received a notification and who confirm that they are not currently on an anticoagulant therapy or are on an anticoagulant therapy that started after enrollment in the study will then be offered an ambulatory ECG monitor (ePatch, BioTelemetry, Inc., Conshohocken, PA). 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 analysis is one hour. 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. This report will then be finally adjudicated by board certified clinicians in a double-adjudication fashion, and a final report will be made available to the Study Telehealth Provider by BioTelemetry.

A second follow-up visit (telephone/video), Study Visit #2, will occur with the Study Telehealth Provider once the ambulatory ECG monitor results are available. 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 during Study Visit #1, 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)

90 days after the irregular pulse notification, only those participants who received an irregular pulse notification will receive a separate app notification to complete the patient reported outcomes (PRO) questionnaire within the app. 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 related to the notification. Participants will receive reminders via notifications from the app to complete the 90-day PROs prior to the due date.

All enrolled participants, regardless of whether or not they received an irregular pulse notification, will receive an End Of Study (EOS) PRO questionnaire towards the end of the study. Those who do not receive a notification will receive the EOS PRO on September 1, 2018. Those who do receive a notification will receive the EOS PRO on January 2, 2019.This

questionnaire will be administered through a website, and participants will have until the end of study to complete. Participants will receive reminders via notifications from the app to complete the EOS PROs prior to the due date. This questionnaire will include questions on whether or not they were diagnosed with AF, started an anticoagulant medication, had any new symptoms during the monitoring period including palpitations, dizziness, fatigue, or had any major gastrointestinal or cerebrovascular bleeding. For those who indicated a new diagnosis of AF, further questions regarding additional treatments or diagnostic tests will be asked.

4.2 Rationale for Study Design

The study aims to estimate how frequently AF is diagnosed on the basis of a confirmatory ambulatory ECG monitoring in participants who receive an irregular pulse notification, and to validate the concordance of the spot tachograms and the IPNA algorithm with cardiac arrhythmias detected by simultaneous ambulatory ECG monitoring. To reach the required number of participants who receive a clinical diagnosis and undergo simultaneous ambulatory ECG patch monitoring, a large number of participants will need to be enrolled, given the relatively low rate of undiagnosed AF in our target population.

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 11.0 or later defined as iPhone model/iOS version used to complete screening eligibility.

    II. Apple Watch (Series 1 or later) with watchOS version 4.0 or later defined as Apple Watch model/watchOS paired with iPhone used to complete screening eligibility.

2. Age ≥ 22 years at time of eligibility screening, ascertained from self-reported date of birth.

3. 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.

4. Proficient in written and spoken English, defined by self-report of comfort reading, writing, and speaking English on iPhone.

5. Valid phone number associated with iPhone, ascertained from self-report.

6. Valid email address, ascertained from self-report.

5.2 Exclusion Criteria

1. Self-reported diagnosis of Atrial Fibrillation at the time of consent.

2. Self-reported diagnosis of Atrial Flutter at the time of consent.

3. Currently on anticoagulation therapy, as self-reported at the time of consent.

6.0 STUDY DEVICE

Device Name: Apple Heart Study app

The Apple Heart Study app is a mobile medical app that analyzes pulse rate data. The app identifies episodes of irregular heart rhythms consistent with atrial fibrillation and other arrhythmias.

Device Description:

The Apple Heart Study app is an application that analyzes heart rate (HR) and beat-to-beat data captured by the Apple Watch photoplethysmogram (PPG) sensor. The Apple Heart Study app uses this data to identify irregular heart rhythms consistent with atrial fibrillation and other arrhythmias. Analysis is initiated when the Apple Heart Study app successfully retrieves approximately one minute of beat-to-beat intervals, defined as a tachogram, derived from the Apple Watch PPG HR sensor through HealthKit, a data repository on a user's iPhone.

In practice, tachograms are collected and stored at selected times throughout the day when a user appears to be still enough for a successful reading to be taken. If, and when, the Apple Heart Study app retrieves a tachogram and subsequently classifies it as "irregular", it shifts into a "confirmation mode" and begins requesting, and analyzing, tachograms on a more frequent basis until it is able to confirm sustained irregularities or the confirmation cycle is otherwise ended.

Upon completion of a positive confirmation cycle within a 48-hour period, the Apple Heart Study app provides a notification to the user on their Apple Watch and subsequently on their iPhone app.

While the app is able to identify irregular heart rhythms consistent with atrial fibrillation and other arrhythmias, the app is not intended to diagnose atrial fibrillation, and any irregular readings or subsequent notifications displayed by the app should be confirmed by ECG and/or by a clinician. The app is not intended to be used on an on-demand basis and should not be used to guide medical therapy decisions.

The Apple Heart Study app is not intended as an implant but rather is stand-alone software that runs on general purpose platforms (the Apple iPhone and Apple Watch). The Apple Heart Study app is also not claimed or otherwise represented to be for a use in supporting or sustaining human life. The Apple Heart Study app is further not intended for use in diagnosing, curing, mitigating or treating disease, as the app is not an atrial fibrillation diagnostic device and should not be used to guide medical therapy decisions. Finally, the Apple Heart Study app does not present a potential for serious risk to the health, safety, or welfare of a participant as the app only serves as a method to detect irregular heart rhythms and

notify users of sustained pulse irregularities that must ultimately be confirmed by an ECG and/or a clinician.

7.0 STUDY PROCEDURES

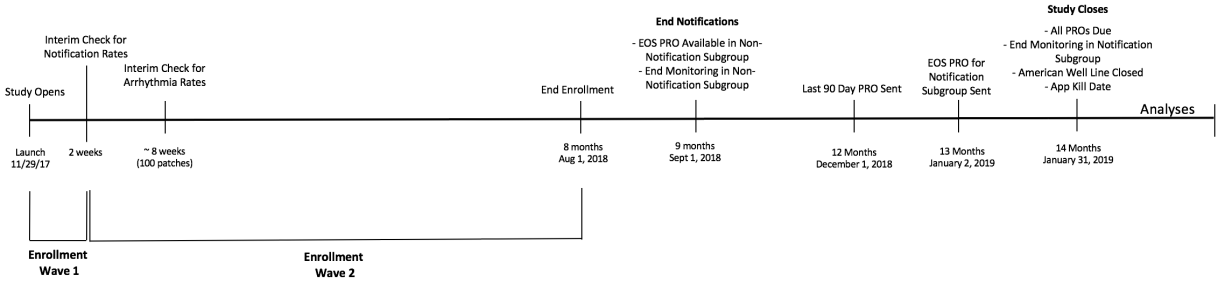

Figure 1. Study Timeline

7.1 Eligibility Determination and Enrollment

The potential participant will first download the Apple Heart Study 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 may continue to the "waiting period", based on the enrollment metering schema and study infrastructure capacity, until it is time for them to consent and enroll. The waiting period for each participant will end once they are able to enroll based on the enrollment metering schema and study infrastructure capacity. After the waiting period, before the potential participant can initiate the consenting process, the participants will be asked to re-confirm their eligibility. Upon responding, they will be presented with an in-app consent and authorization form to be read and signed if they agree to participate.

The study anticipates a very large volume of participants to be screened and consented in the initial days following study opening. There is a potential risk of overwhelming the study infrastructure if all participants are allowed to enter the study monitoring phase instantly.

To maintain operational efficiency, the study will use an enrollment metering schema, whereby participants who are eligible for inclusion may be delayed in consent and enrollment (baseline characterization, and initiation into the monitoring portion of the study). Participant safety will be monitored through interim checks (see Section 11.5 below).

Enrollment metering will be adaptable based on study and clinical bandwidths, with metering instituted by invitation to consent. Once consent is obtained, enrollment and initiation of monitoring for pulse irregularity will commence. Initial enrollment will be heavily weighted towards enrollment of a population more likely to be at risk for undiagnosed AF, such as those over age 65 years.

Pre-planned enrollment metering strategy will include two enrollment waves:

1. Wave 1: Weighted enrollment

   During the first two weeks that the study is open, approximately 1000 new participants aged $\geq$ 65 years will be enrolled per week, and approximately 700 participants aged 22-64 years will be enrolled per week.

2. Wave 2: Open enrollment

   Two weeks after the start of Wave 1, enrollment metering of all eligible participants will be based on notification rates and as study infrastructure allows.

7.1.1. Expected Enrollment and Study Participant Timeline

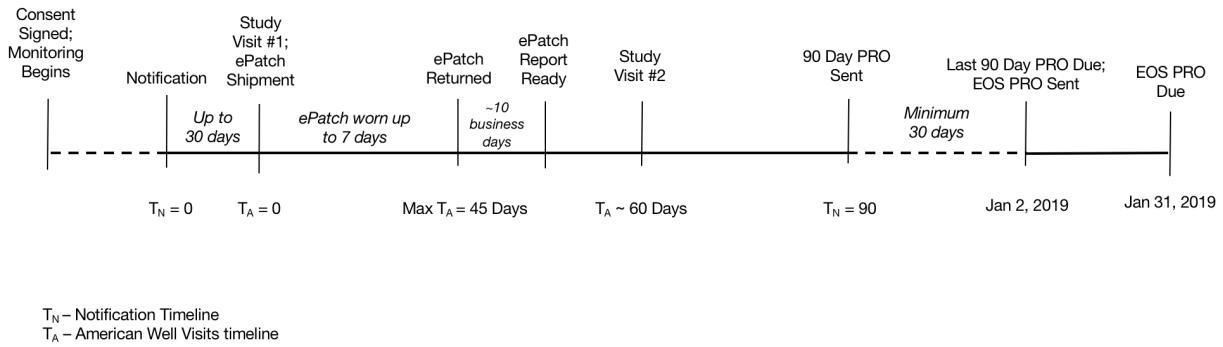

Figure 2. Participant Level Flow Chart

We expect to reach our full enrollment target within the first nine months following study opening on November 29, 2017. Participants will be able to enroll between November 29, 2017, and August 1, 2018.

On August 1, 2018, enrollment will close. On September 1, 2018, no further irregular pulse notifications will be sent. Monitoring will end on September 1, 2018 in participants who never received a notification, and the EOS PRO will become available to this group.

Participants who receive a notification of an irregular pulse from their app will continue to be monitored until the end of study for the purpose of data collection for the concordant Apple Watch and ECG patch monitoring analyses. A 90-day PRO will become available 90 days after notification, no later than December 1, 2018. The EOS PRO will become available to the notification subgroup on January 2, 2019.

All PROs will be due by end of study on January 31, 2019. After this date, all monitoring will end, the American Well line will be closed and no further data will be collected.

7.2 Enrollment: Consent, Baseline Demographics and Medical History Collection

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

The approach to informed consent for the AHS 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 an AHS hotline (available 24/7 at 1-844-606-1609) 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. The participant will be considered ‘enrolled’ from this point and the study app monitoring of Apple Watch PPG sensor data will begin thereafter.

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

7.3 Overall Procedures for Enrolled Participants: Monitoring Initiation and Patient Reported Outcomes

After completing the baseline demographics and medical history questionnaires within the app, the participant will wear their Apple Watch as per normal usage with the IPNA analyzing intermittent passively collected PPG pulse data, with two possible outcomes:

1. No pulse irregularities that meet the IPNA notification threshold are identified from the time monitoring begins (after consenting) to September 1, 2018.

   or;

2. Pulse irregularities are identified by the IPNA that meet notification threshold during the study. The participant is then notified via the app of this irregularity. Participants who receive a notification during the study will enter the positive notification workflow [see 7.4.1 Monitoring Workflow - Positive Notification].

All study participants who do not actively withdraw, and who do not receive an irregular pulse notification, will be invited to complete a web-based EOS PRO survey on September 1, 2018 and participants can complete this survey any time before January 31, 2019 [see 7.5 PRO Instruments].

7.4 Monitoring Flow

7.4.1 Monitoring Flow - Positive Notification

After the participant receives a pulse irregularity notification within the Apple Heart Study App:

1. The app notification will provide a button for the participant to connect with the Study Telehealth Provider. Participant will be instructed to contact the Study Telehealth Provider and be informed that they will receive no further **irregular pulse notifications**, even if pulse irregularity that meets IPNA notification threshold occurs at any time point until the study end.

2. If the participant does not connect with the Study Telehealth Provider within 24 hours of receiving the original notification, the participant will continue to receive in-app **reminder notifications** daily for 14 consecutive days following the initial notification. The reminder will include an alert indicating a possible irregular pulse and that they should connect with the Study Telehealth Provider. The first connection with the Study

Telehealth Provider will constitute Study Visit #1 [see 7.4.2 Study Telehealth Provider Service Workflow].

3. If no connection is made with the Study Telehealth Provider within 30 days, participant will be placed in a fall-out subgroup. After 14 days, the app on participant's phone will send no further reminder notifications or irregular pulse notifications. Those in the fall-out subgroup will receive the positive-notification PRO survey at 90 days following initial notification and EOS PRO on January 2, 2019.

The study team may contact participants who receive the irregular pulse notification in order to remind participants to connect with the Study Telehealth Provider.

7.4.2 Study Telehealth Provider Service Workflow

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 patients 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. 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- and HIPAA-compliant, 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 at visit #1 and #2. All OCG physicians are licensed, board certified, and 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 Online Care Group'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, Level 1 agents operating the 24-hour hotline and the Network Operating Center (NOC) staff who coordinates efforts to initiate shipment of the ambulatory ECG monitoring

patch and facilitates the communication of patch report results and clinical summaries to the participant. All these groups provide services through American Well platform.

After the participant connects with the Study Telehealth Provider team, they will undergo:

1. **Study Visit #1:**

   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. Those with emergent symptoms will be moved to the fall-out subgroup and still receive a positive-notification PRO survey at 90 days. These participants will not receive the ambulatory ECG monitors.

   Once emergency symptoms have been ruled out, the telehealth clinician will perform a standard review of medical history, confirm that the subject is not on anticoagulant therapy or is on anticoagulant therapy that started after enrollment in the study, and perform a virtual review of physical symptoms. The information obtained will assure that the Study Telehealth Provider Data Collection variables [see 7.4.3 Study Telehealth Provider Data Collection] are obtained. The Study Telehealth Provider will provide the participant information about the ePatch to those who have confirmed that they are not on anticoagulant therapy or are on anticoagulant therapy that started after enrollment in the study, answer any questions the participant might have and contact BioTelemetry to initiate the order and shipment of the ambulatory ECG monitor (ePatch). 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 interpretation 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 extremely rare, this includes sustained ventricular tachycardia or ventricular fibrillation, high-degree heart block, and long pauses. If one of these life-threatening 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 life-threatening arrhythmias, the ambulatory ECG study will be processed into the adjudication workflow. The adjudication workflow is described in a separate charter.

The adjudication process will result in generation of a final adjudicated report. Once the adjudicated report is complete, it will be issued to the Study Telehealth Provider. When the Study Telehealth Provider receives this final adjudicated report from BioTelemetry, 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 to conduct Study Visit #2.

2. Study Visit #2:

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.

The research team may contact participants to ensure that participants complete all study-related visits and procedures or for other purposes as deemed necessary by the investigators.

7.4.3 Study Telehealth Provider Data Collection

Study Visit #1:

The following data elements will be collected during visit intake or during the visit:

1. Demographics
2. Past medical history
3. Medications
4. Symptoms
5. Clinical assessment
6. Complaints

Study Visit #2:

The following data elements will be collected:

1. Symptoms during ECG monitoring period
2. Actions taken by participant since initial visit
3. Clinical assessment
4. Complaints

7.4.4 BioTelemetry ePatch Monitoring

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.

Study Visit #1:

During Study Visit #1, participants will receive brief instructions on ePatch, get any of their questions on ePatch answered and be notified that an ePatch will be mailed to them within approximately 5 days.

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.

After Initial Visit:

Approximately 14-20 days after the Visit #1 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 the date of Study Visit #1. Those who return patches beyond 45 days 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 ePatch will also be placed in the fall-out subgroup.

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 Study Telehealth Provider will notify the participant 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. This visit will occur approximately 60 days following Visit #1, but will vary depending on the time it takes the participant to wear and return the ePatch. During this visit, results of ambulatory ECG monitoring will be reviewed and further clinical care options will be discussed. 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 the Study Telehealth Provider information of participant's physician and permission to send that physician a copy of the report.

7.5 PRO Instruments

7.5.1 90-Day PRO

Participants who receive an irregular pulse notification will be notified by alert via the Apple Heart Study app to complete the 90-day PRO questionnaire at 90 days following their irregular pulse notification. The questionnaire will be administered through the Apple Heart Study app, and the participant will have until January 31, 2019, to complete it. Participants will receive reminders via notifications from the app to complete the EOS PROs prior to the due date. 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, and whether the participant experienced any anxiety as a result of participation.

7.5.2 End of Study (EOS) PRO

For those who do not receive an irregular pulse notification, the End of Study (EOS) PRO will become available to complete on September 1, 2018. All enrolled participants who received an irregular pulse notification during the monitoring period, prior to September 1, 2018, will be notified instead on January 2, 2019 to complete the EOS PRO questionnaire. The EOS PRO will be available via a link in the app to a website where the EOS PRO questionnaire will be administered. Participants will have up until January 31, 2019, to complete this questionnaire. Participants will receive reminders via notifications from the app to complete the EOS PROs prior to the due date. Questions will cover whether, during the study period, the participant received a diagnosis of AF, they received treatment for their AF, and whether the participant experienced any anxiety as a result of participation.

7.6 Time and Events Schedule

Evaluation	Screening and Eligibility	Consent and Enrollment	Study Visit #1 (≤ 30 days after notification)	Study Visit #2 ~60 days after Visit #1	90 Day PRO	End of Study PRO
All Participants						
Inclusion/ Exclusion Criteria	**X**					
Informed Consent	**X**	**X**				
Demographics/ Medical History		**X**				
Survey Completion						**X**
Notification Subgroup						
Virtual Review of Medical History / Physical Symptoms			**X**			
Ambulatory ECG Monitor - Introduction/ Shipment			**X**			
Ambulatory ECG Monitor - Results Review				**X**		
Arrhythmia Recommendations for PCP referral				**X**		
Survey Completion					**X**	

7.7 Fall-out Subgroup

The fall-out subgroup will include participants who received a notification, but provide incomplete data for various reasons. The reasons may include:

1. Failure to call Study Telehealth Provider within 30 days after notification.

2. Urgent symptoms discovered during Study Visit #1 virtual medical evaluation by Study Telehealth Provider requiring immediate direction to EMS (urgent care clinic or emergency room) for medical care.

3. Failure to return an ePatch within 45 Days after Visit #1.

8.0 STUDY OUTCOMES

1. Atrial fibrillation $\geq$ 30 seconds ascertained by ambulatory ECG monitoring,

2. Concordant AF (any duration) detected simultaneously by spot tachogram from PPG based pulse irregularities and ambulatory ECG monitor.

3. Concordant AF (any duration) detected simultaneously by positive IPNA from PPG based pulse irregularities and ambulatory ECG monitor.

4. Self-reported participant contact with health care provider within 3 months after irregular pulse notification.

5. Patient reported outcomes (PRO) collected:

    1. 90 days after notification of pulse irregularity, and/or
    2. At the end of study (EOS).

9.0 ADVERSE EVENTS REPORTING

All suspected adverse events (AEs) will be reported to the Study Safety Monitoring Desk by the Study Telehealth Provider Team. The Study Safety Monitoring Desk will review suspected AEs and determine whether they are adverse device effects (ADEs).

9.1 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 investigational device.	ISO 14155-1
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. Notes: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical 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

Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.	21 CFR 812.3(s)

9.2 Adverse Events (AEs)

Adverse events that will be collected do not have to be related to use of the investigational device, ePatch, iPhone, or Apple Watch. The Study Safety Monitoring Desk is responsible for determining whether the adverse event is associated with the investigational device, and would therefore be considered an "adverse device effect."

Possible AEs related to participation in the study, but not related to use of the investigational device, 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.

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 IPNA notification;
- Detection of atrial fibrillation or other irregular heartbeat through the IPNA and confirmation by 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 as described by the Study Telehealth Provider.
- Apple Heart Study app functionality issues related to poor wifi or cellular connectivity or user error

9.3 Adverse Device Effects (ADEs)

ADEs are those effects determined by the Study Safety Monitoring Desk to be related to use of the investigational device, the Apple Heart Study app.

Anticipated ADEs include the following:

- Signs or symptoms related to participation in the study, including those determined to be related to the Apple Heart Study app. 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.

9.4 Recording of Adverse Events (AEs) and Adverse Device Effects (ADEs)

All suspected AEs will be recorded by the Study Telehealth Provider Team during the scheduled virtual visits as well as at any time point during the study where the participant or their representative contacts the Study Telehealth Provider to report such an event. The Study Safety Monitoring Desk personnel will assess suspected AEs for classification as suspected ADEs. All suspected AEs and ADEs will be tracked by the Study Safety Monitoring Desk personnel and all suspected ADEs will be reviewed and classified by the Study Safety Monitor.

9.5 Recording of Serious Adverse Events (SAEs)

All suspected SAEs will be recorded by the Study Telehealth Provider Team during the scheduled virtual visits as well as at any time point during the study where the participant or their representative contacts the Study Telehealth Provider to report such an event. The Study Safety Monitoring Desk personnel will track all SAEs and all SAEs that are potentially ADEs will be reviewed and classified by the Study Safety Monitor.

9.6 Reporting of Serious and Unanticipated Adverse Device Effects (UADEs)

For this non-significant risk (NSR) study, the Investigators will be responsible for reporting any unanticipated adverse device effects (UADEs), as required by the IRB's procedures and in conformance with FDA regulatory requirements. Reporting requirements as per 21 CFR 812.150 will be followed for this study.

All UADEs shall be reported to the sponsor and reviewing IRB as soon as possible, but no later than 10 working days after the Study Safety Monitoring Desk's confirmation of the event as an UADE. IRB reporting will be performed according to governing IRB requirements.

The Principal Investigators are responsible for informing the IRB of any UADE and submit a copy of the report to the sponsor within 5 working days.

The study sponsor will conduct an evaluation of a UADE under 812.46(b) and report the results of such evaluation to FDA within 10 working days after the sponsor first receives notice of the effect.

10.0 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.

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 received a notification, and 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

11.0 STATISTICAL CONSIDERATIONS

11.1 Analysis Sets

The Full Analysis Set (FAS) will consist of all participants who are enrolled in the study.

The Notification Analysis Set (NAS) will consist of all participants who receive a IPNA. This analysis set is equivalent to the Notification Subgroup. The co-primary AF endpoint will be collected from these participants to evaluate Objective 1.

The ECG Analysis Set (EAS) will consist of all participants who receive an ambulatory ECG monitor, wear it for a minimum amount of time providing a minimum analyzable time of 1 hour, and self-report no history of AF prior to the time of consent. This analysis set includes all participants in the ambulatory ECG monitor subgroup who wear their patch providing at least 1 hour of analyzable time. The co-primary tachogram endpoint will be collected from these participants to evaluate Objective 2. All tachogram- and alert-level outcomes will be estimated from this analysis set during times when tachograms are being recorded by Apple Watch during simultaneous, analyzable ECG monitoring. The ambulatory ECG monitor recordings will be measured during the entire period the patch is worn.

11.2 Endpoints and Definitions

11.2.1 Co-Primary Endpoints

1. AF of greater than 30 seconds duration detected on ambulatory ECG monitoring for a participant who received an irregular pulse watch notification.
2. Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with AF during time intervals when the spot tachogram is positive for an irregular pulse among those who received a notification. Each participant contributes multiple observations for this endpoint.

11.2.2 Secondary Endpoints

1. Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with AF when the IPNA based on multiple tachograms is positive for an irregular pulse among those who received a notification. These positive IPNA triggers will not result in additional notifications to participant, but will be available for analyses. Each participant contributes multiple observations for this endpoint.
2. Self-reported contact with a health care provider within 3 months following an irregular pulse watch notification.

11.2.3 Tertiary Endpoints

1. Arrhythmias, other than AF, detected on an ambulatory ECG monitor that can also result in an irregular pulse. These include sinus arrhythmia, frequent premature atrial contractions, frequent premature ventricular contractions, intermittent heart block, multifocal atrial tachycardia and atrial tachycardia with variable conduction.
2. AF of greater than 6 minutes, 1 hour, 6 hours, and 24 hours duration detected on ambulatory ECG monitor following an irregular pulse watch notification.
3. Self-reported initiation of therapies for AF, including anticoagulant, rate-controlling and antiarrhythmic therapy.
4. Self-reported electrical or chemical cardioversion by a health care provider.

11.3 Statistical Approaches

11.3.1 Estimating Positive Predictive Value (PPV) in the First Objective

We have designed the study to estimate the proportion of participants age 65 or older diagnosed with AF within a 5% margin of error. In other words, we have designed the study so the 97.5% confidence interval around the estimate will have a width of 10%. Our analysis will include the participants 65 or older in the NAS. There is no hypothesis testing for the co-primary outcomes. We use 97.5% confidence intervals to account for the co-primary outcomes.

11.3.2 Estimating PPV of the Spot Tachogram to Address the Second Objective

We assume that each tachogram measured on a participant is independent of other intervals measured from that participant. In sensitivity analyses, we will evaluate the impact of this assumption. From the available intervals, we will randomly select 10 intervals per participant in the EAS to ensure each participant contributes a comparable period of data on which to evaluate concordance. All intervals will be used in participants who have fewer than 10 intervals available.

We will conclude that the algorithm may be promising if the PPV is extremely high. Our hypothesis is that the proportion of intervals that are true positives out of the total intervals where the spot tachogram is positive for an irregular pulse will be at least 0.75 in participants 65 or older. We will design our study so that we will have ~99% power to detect whether the lower bound of a 97.5% confidence interval is greater than 0.70 and the upper bound is at least 0.75 if the PPV is truly 0.75. The power will increase if the PPV is higher than 0.75 in reality.

11.3.3 Secondary and Tertiary Analyses

All secondary and tertiary outcomes will be analyzed as proportions with 95% confidence intervals. Outcomes measured at the tachogram- or alert-level will be analyzed in the EAS while self-reported contact with a health care provider and initiation of therapies or cardioversion will be analyzed in the NAS. The self-reported outcomes will also be analyzed in the FAS.

11.3.4 Sensitivity and Sub-Analyses

As a sensitivity analysis, the estimates for the co-primary outcomes will be repeated for participants of all ages.

The proportions and 97.5% confidence intervals used to analyze the co-primary outcomes will be performed separately by age (<55, 55-64, ≥ 65), AF burden, type of AF and non-AF irregular rhythms. Additionally, we will perform chi-squared tests to test whether the PPV proportions differ by age or burden.

To better understand the performance of the IPNA across the participant population, we will construct separate 95% confidence intervals around the proportion of participants diagnosed with AF according to tertiles of spot tachogram PPV observed in the secondary objective.

11.4 Handling of Missing Data

All participants who receive a positive IPNA will be included in the analysis of the co-primary endpoint indicating AF after positive IPNA regardless of whether they receive and wear the ambulatory ECG monitor. Participants who do not have at least an hour of analyzable wear time from the ambulatory ECG monitor will be considered to have missing data. Multiple imputation methods will be used to account for the participants who are missing the AF endpoint.

In analyses where the tachogram or an IPNA is the unit of analysis, participants who have at least one tachogram recorded during the simultaneous ECG monitoring will be including in the analyses. We will use any available tachograms and no data will be considered missing.

Multiple imputation methods will be used in the analyses of patient reported outcomes to account for an expected small proportion of participants who do not complete all questions.

11.5 Interim Checks

A series of interim checks will be performed.

Throughout the course of the study, the number of irregular pulse watch notifications occurring per age subgroup will be checked. A check will be performed 2 weeks after the first participant is enrolled (see Figure 1. Study Timeline). If a high number of alerts is observed (greater than 10%), enrollment may be paused or throttled downward in any age subgroup (<40, 40-54, 55-64, ≥65). If the number of notifications observed is less than the study infrastructure capacity, the numbers of participants invited to enroll from the "waiting period" may be increased.

An interim check will be performed upon completion of the first 100 ambulatory ECG monitors in any of the four age subgroups (see Figure 1 Study Timeline). The interim check will be performed for each subgroup regardless of how many patches are received in other age subgroups. We estimate the check to occur at approximately 6-8 weeks after the first participant enrolled to check the following:

1. At least 50% of participants notified of an irregular pulse are ultimately wearing and returning the ambulatory ECG monitor. A low rate of ambulatory ECG monitor use would result in an increase in the rates of invitations to enrollment in any age subgroup.

2. Percentage of atrial fibrillation noted on ambulatory ECG monitoring is greater than 1%. A detection of atrial fibrillation less than 1% will prompt a cessation of enrollment in any corresponding age subgroup.

3. Percentage of non-clinically relevant irregular rhythms is greater than 90%. If the vast majority of rhythms detected on ambulatory ECG monitoring are due to other irregular, non-AF arrhythmias, such as sinus arrhythmia, frequent PACs and frequent PVCs, this will prompt a cessation of enrollment in any corresponding age subgroup.

The co-primary endpoints will be evaluated after 503 participants aged ≥65 have completed their virtual visit and have at least 1 hour of ambulatory ECG monitor data recorded, i.e. at least 503 participants who are in the EAS.

These interim analyses are not designed to evaluate ultimate efficacy or futility and do not impact the Type I error as we will not be examining the final positive predictive values of the co-primary endpoints using this interim analysis.

A much higher than anticipated rate of notifications and subsequent ePatch evaluations may result in marginal benefit of additional participant enrollment. The following will be set as

maximum targets for ePatch monitoring. Exceeding these limits will trigger either a throttling downward or cessation of enrollment:

1. Completion of 5,000 ePatches in total in either participants ≥ 65 or participants aged 22-64 will result in cessation of enrollment in the corresponding age group.

2. Completion of > 100 ePatches per week in either participants ≥ 65 or participants aged 22-64 will result in a throttling downward of enrollment invitations in the corresponding age groups.

11.6 Sample Size and Power Considerations

We anticipate identifying 750 participants age 65 or older who qualify for an ePatch during the initial study period of 3 months. Among these, we anticipate a clinical diagnosis will be available on 503 participants. The proportion of participants with clinically important AF will be estimated and a 97.5% confidence interval will be constructed around the estimate. Similarly, a 97.5% confidence interval will be constructed for the estimated proportion of participants with clinically important AF among those who receive an irregular pulse watch notification of all ages. With 503 participants, we will have sufficient observations to estimate the proportion with a margin of error of 5% or smaller, regardless of what the true proportion is.

Our decision rule for concluding the IPNA is promising to address Objective 2 is sensible given the amount of data with which we will rule our algorithm as promising or in need of greater refinement. With 3000 observed intervals where ePatch and tachogram data is available in participants 65 or older, we will have at least ~98% power to rule out a PPV of 0.70 or lower (using the decision rule and assumptions described in Section 11.3.2).

If we assume that we will sample 10 intervals from each person with an ePatch, then we will need 300 participants with ePatches to get 3000 observed intervals, which is well below the 503 participants required for the AF co-primary endpoint.

We are assuming that 1% of participants 65 and older will get a notification and receive an ePatch, which corresponds to 75,000 participants older than 65 needed to enroll in the study to achieve sufficient power. We additionally plan to enroll approximately 425,000 participants aged less than 65 during the study period. We are making the conservative assumption that ~2 participants out of 1000 in the younger age group will qualify to receive an ambulatory ECG monitor, from which we expect 503 participants to have data available from their ambulatory ECG monitor.

12.0 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.

13.0 STEERING COMMITTEE AND DATA AND SAFETY MONITORING BOARD

A Steering Committee (SC) will be commissioned to monitor the practical aspects of the study and to provide independent scientific guidance regarding the protocol, implementation, execution and analysis. SC will perform periodic review of the study progress, recruitment figures, data, data quality, analysis and results. SC will resolve any differences within the research team or between research team and the sponsor on the data management or study procedures and will provide recommendations for modifications to the protocol if needed.

An independent Data and Safety Monitoring Board (DSMB) will be appointed and will report to the Steering Committee. The DSMB will be responsible for safeguarding the interests of the participants and for reviewing the overall conduct of the clinical study. The DSMB charter will be prepared to detail precise roles and responsibilities and procedures and interactions with the Steering Committee.

14.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with FDA regulations (21 CFR Parts 50, 54, 56 and 812).

14.1 Institutional Review Board/Medical Ethics Committee

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.

14.2 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.

14.3 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 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.

15.0 HUMAN SUBJECTS PROTECTION

15.1 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.

15.2 Compensation to participants

There will be no direct monetary remuneration to study participants.

16.0 RECORD KEEPING/REPORTING

16.1 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, data on watch PPG detected pulse irregularities, ambulatory ECG monitor results, Adverse Events and 90-day PRO.

16.2 Study Documentation

Study documentation includes but is not limited to all consent forms, app screens, app based screening forms, 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.

17.0 REFERENCES

1. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation.* 2006;114(2):119-125.
2. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res.* 2014;114(9):1453-1468.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med.* 1987;147(9):1561-1564.
4. Writing Group M, Mozaffarian D, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation.* 2016;133(4):e38-360.
5. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA.* 2002;288(19):2441-2448.
6. Lin HJ, Wolf PA, Benjamin EJ, Belanger AJ, D'Agostino RB. Newly diagnosed atrial fibrillation and acute stroke. The Framingham Study. *Stroke.* 1995;26(9):1527-1530.
7. Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise screening of atrial fibrillation in a 75-year-old population: implications for stroke prevention. *Circulation.* 2013;127(8):930-937.
8. Cullinane M, Wainwright R, Brown A, Monaghan M, Markus HS. Asymptomatic embolization in participants with atrial fibrillation not taking anticoagulants: a prospective study. *Stroke.* 1998;29(9):1810-1815.
9. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(12):3754-3832.
10. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37(38):2893-2962.
11. Turakhia MP, Shafrin J, Bognar K, et al. Economic Burden of Undiagnosed Nonvalvular Atrial Fibrillation in the United States. *Am J Cardiol.* 2015;116(5):733-739.
12. Lowres N, Neubeck L, Salkeld G, et al. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost.* 2014;111(6):1167-1176.
13. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. *Circulation.* 2015;131(25):2176-2184.
14. Tung CE, Su D, Turakhia MP, Lansberg MG. Diagnostic Yield of Extended Cardiac Patch Monitoring in Patients with Stroke or TIA. *Front Neurol.* 2014;5:266.

15. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med.* 2014;370(26):2467-2477.

Statistical Analysis Plan

Study Official Title: Apple Heart Study: Assessment of Wristwatch-Based Photoplethysmography to Identify Cardiac Arrhythmias

ClinicalTrials.gov Identifier: NCT03335800

Document Date: 09 Nov 2018

Stanford MEDICINE | Quantitative Sciences Unit

Statistical Analysis Plan

Study Name	Apple Heart Study
Version Number	1.6
Date	9 November 2018

Apple Heart Study

Assessment of Wristwatch-Based Photoplethysmography to Identify Cardiac Arrhythmias

SIGNATURE PAGE

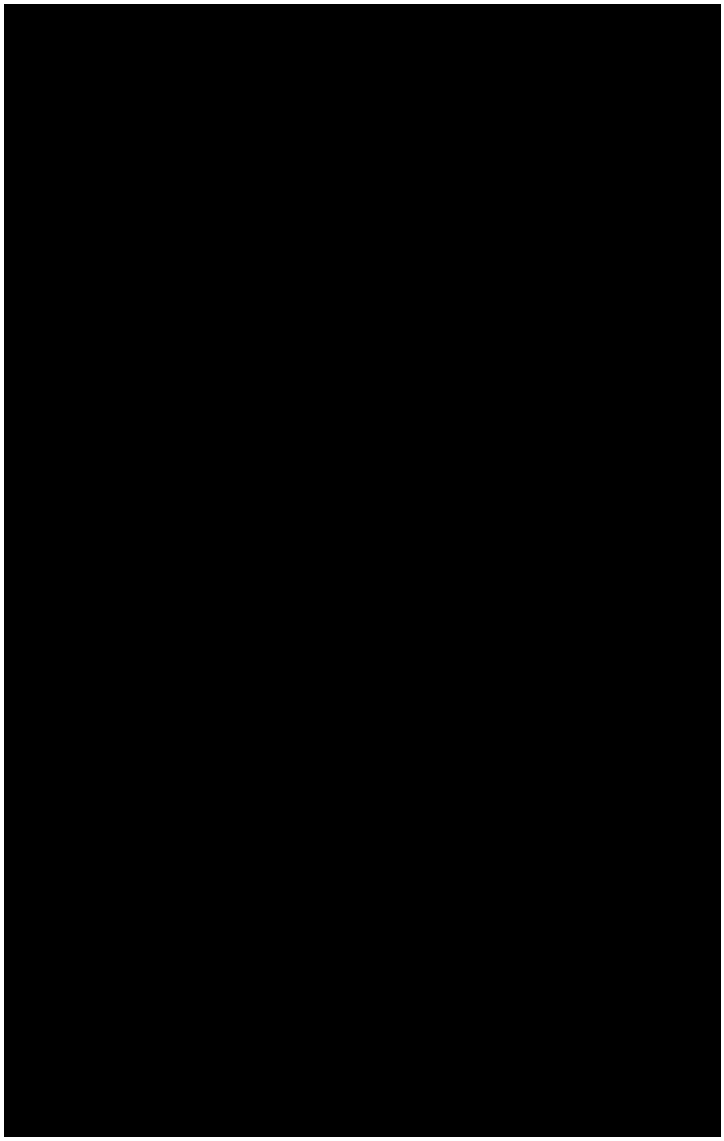

TABLE OF CONTENTS PAGE

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
ARR	Arrhythmia
CI	Confidence Interval
EAS	ECG Analysis Set
ECG	Electrocardiography
FAS	Full Analysis Set
IPN	Irregular Pulse Watch Notification
IPNA	Irregular Pulse Watch Notification Algorithm
NAS	Notification Analysis Set
PAC	Premature Atrial Contractions
PCP	Primary Care Provider
PPG	Photoplethysmography
PPV	Positive Predictive Value
PRO	Patient Reported Outcome
PVC	Premature Ventricular Contractions
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Revision history

Revision	Date	Section/Page	Changes Made -- Reasons for the Change
1	4/19/18	Throughout document	Added table shells
2	4/19/18	Section 1.1/Page 6	Updated text of Objective 3 to be consistent with protocol v8.0
3	4/19/18	Section 1.2/Page 7	Defined ECG acronym in text
4	4/19/18	Section 2.3, 4.4/Page 9, 18	Updated tertiary endpoint to be consistent with protocol v8.0
5	4/19/18	Section 3/Page 10	Updated definitions of analysis sets for clarification and to reflect protocol amendment in v8.0
6	4/19/18	Section 4.3/Page 17	Clarified analysis sets in tertiary analyses
7	4/19/18	Section 4.4/Page 20	Updated definition of fall-out subgroup to be consistent with protocol v8.0
8	4/19/18	Section 5/Page 25	Updated interim checks text to be consistent with protocol v8.0
9	5/24/18	Section 4.2/Page 14	Updated categories in Table 2 to be consistent with options available in app
10	5/24/18	Section 6/Page 27	Added validation plan and appendix containing sub-study protocol and SAP
11	5/31/18	Section 4.4/Page 19	Added resampling to characterize uncertainty of confidence interval estimates
12	11/9/18	Section 1.3, 4.3/Page 8, 17	Updated tachogram sampling plan

INTRODUCTION

This statistical analysis plan (SAP) is a comprehensive and detailed description of the strategy, rationale and statistical techniques that will be used to assess and evaluate the ability of the Irregular Pulse Watch Notification Algorithm (IPNA) to identify atrial fibrillation and atrial flutter (AF) and guide subsequent clinical evaluation.

1. STUDY DETAILS

1.1 Study objectives

Objective 1a: To measure the proportion of participants aged ≥ 65 with irregular pulse watch notifications who have demonstrable AF as confirmed by ambulatory electrocardiographic patch monitoring.

Objective 1b: To measure the proportion of all participants with irregular pulse watch notifications who have demonstrable AF as confirmed by ambulatory electrocardiographic patch monitoring.

Objective 2: To characterize the concordance between pulse irregularity determined using spot tachograms (approximately one minute of beat-to-beat intervals) and AF detected by simultaneous ambulatory electrocardiographic patch monitoring.

Objective 3: To estimate the rate of initial contact with a health care provider within 3 months after an irregular pulse notification.

1.2 Study design

This will be a prospective, single arm, experimental study using participants wearing an Apple Watch with the Apple Heart Study app. 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) within the Apple Heart Study app. The algorithm's analysis is initiated when the Apple Heart Study app successfully retrieves approximately one minute of beat-to-beat intervals, defined as a tachogram, derived from the Apple Watch PPG HR sensor through HealthKit, a data repository on a user's iPhone. If, and when, the Apple Heart Study app retrieves a tachogram

and subsequently classifies it as "irregular", it shifts into a "confirmation mode" and begins requesting, and analyzing, tachograms on a more frequent basis until it is able to confirm sustained irregularities or the confirmation cycle is otherwise ended. Upon completion of a positive confirmation cycle within a 48-hour period, the Apple Heart Study app provides a notification (IPN) to the user on their Apple Watch and subsequently on their iPhone app.

Participants without urgent symptoms who receive an irregular pulse notification will be offered an ambulatory electrocardiographic (ECG) monitor (ePatch). Participants will be requested to wear the ePatch for 7 days. An independent team of board certified clinicians will adjudicate the technical report generated from the ePatch monitoring to identify periods of AF and other rhythm irregularities. Additionally, this team will adjudicate the raw ECG data that is matched to the time period of the individual tachograms.

Participants who receive an irregular pulse notification (IPN) will receive an additional request to enter participant reported outcomes (PRO) three months after the notification. All participants, regardless of whether they received an irregular pulse notification (IPN), will receive an end-of-study PRO questionnaire at the end of the study, which is anticipated to be approximately one year after initial Apple Heart Study App availability.

1.3 Number of Participants Needed to Address Objectives

The minimum number of ePatches needed was calculated based on our desire to estimate the proportions in Objectives 1a and 1b such that the 97.5% confidence interval around the estimate is no wider than 0.10 in both age groups (< 65 and ≥ 65). We derived the number of enrolled participants and the number of tachograms needed from the number of ePatches required to achieve our desired precision in Objectives 1a and 1b.

The feasibility of our study relies on an assumption that 1% of participants 65 and older will receive a notification and that approximately ⅔ of those receiving a notification will return their ePatch and receive a clinical diagnosis. This corresponds to 75,000 participants older than 65 needed to enroll in the study to achieve sufficient precision. We anticipate identifying at least 750 participants age 65 or older who qualify for an ePatch during the initial study period of 3 months. Among these participants, we anticipate a clinical diagnosis (via adjudication of the ECG patch) will be available on 503 participants. The proportion of participants age 65 or older with clinically important AF will be estimated and a two-sided 97.5% confidence interval will be constructed for the probability of clinically important AF in this population (Objective 1a).

We are making the conservative assumption that ~2 participants out of 1000 in the younger age groups (total of all participants in <40, 40-54, 55-64) will qualify to receive an ePatch, from which we expect at least 503 participants to have data available from their ePatch. A two-sided 97.5% confidence interval will be constructed among all participants for the probability of observing clinically important AF among all adults who receive an irregular

pulse watch notification (Objective 1b). With 503 participants, we will have sufficient observations to estimate the probability with a confidence interval width of 0.10 or smaller, regardless of what the true proportion is.

Objective 2 will be devoted to evaluating the concordance between irregularity identified by the spot tachograms and that detected by the ePatch. We will conclude that the algorithm produces clinically meaningful alerts if the PPV is high, where ePatch is considered the gold standard against which to gauge performance of the spot tachograms. We expect that the proportion of intervals that are true positives out of the total intervals where the spot tachogram is positive for an irregular pulse will be at least 0.75 in participants 65 or older. Our decision rule for concluding the IPNA is sufficiently concordant with ePatch is that the lower bound of a two-sided 97.5% confidence interval is greater than 0.70 and the upper bound is at least 0.75. The same decision rule will be applied to analyses performed on participants of all ages.

Our decision rule is sensible given the amount of data with which we will rule our algorithm produces clinically meaningful alerts. The properties of our decision rule are based on observing 3000 tachograms where the ePatch is concurrently available in participants 65 or older. The same decision rule will be applied to analyses performed on participants of all ages. We evaluated the properties of our decision rule using 1000 simulated data sets each with 3000 tachograms. We assumed 2250 (75%) tachograms were concordant with the ambulatory ECG monitoring and constructed the 97.5% confidence intervals using an asymptotic Gaussian approximation. With 3000 observed tachograms where ePatch is concurrently available in participants 65 or older, we will have at least 98% power to detect whether the lower bound of a 97.5% confidence interval is greater than 0.70 and the upper bound is at least 0.75 if the PPV is truly 0.75.

While this is not a traditional hypothesis test, we have set 0.75 as the threshold to be met or exceeded in order to determine if the algorithm produces meaningful alerts. This threshold was chosen as a clinically meaningful parameter for the individual tachogram concordance. This threshold will be applied to analyses performed on participants 65 or older and to analyses including all ages.

Our enrollment plan will allow us to evaluate the appropriate number of tachograms from the appropriate number of participants. Specifically, we will randomly sample at least 10 positive tachograms from each person with an ePatch, requiring at most 300 participants with positive tachograms recorded while wearing ePatches to provide 3000 observed intervals, which is well below the 503 participants required for the AF co-primary endpoint. Based on preliminary data, an average of 4 tachograms per day are expected to be collected in participants with regular rhythms and a higher number in participants with irregular rhythms. Hence, we expect to have at least 10 positive tachograms observed during the simultaneous ECG monitoring period lasting approximately 7 days in most participants being monitored.

2. ENDPOINTS

2.1 Primary Endpoints

The co-primary endpoints of the study are

- An indicator for whether AF of greater than 30 seconds duration was detected on ambulatory ECG monitoring for a participant who received an irregular pulse notification. (AF after IPN)

- Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with AF during time intervals when the spot tachogram is positive for an irregular pulse among those who received a notification. This endpoint will be measured during time intervals when the watch provides tachogram data and the participant has patch data recorded. Each participant contributes multiple observations for this endpoint. (ePatch+)

2.2 Secondary Endpoints

The secondary variables are

- Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with AF of greater than 30 seconds duration when the IPNA based on multiple tachograms is positive for an irregular pulse among those who received a notification. These positive IPNA triggers will not result in additional notifications to participant, but will be available for analyses. Each participant contributes one observation. (IPNA+)
- Self-reported contact with a health care provider within 3 months following an irregular pulse notification. (PCP PRO after IPN)

2.3 Tertiary Endpoints

- An indicator for the presence of arrhythmias other than AF detected on ambulatory ECG monitoring that can also result in an irregular pulse. Arrhythmias considered include sinus arrhythmia, frequent premature atrial contractions (PAC), frequent premature ventricular contractions (PVC), intermittent heart block, multifocal atrial tachycardia, and atrial tachycardia with variable conduction. Definitions of each arrhythmia are provided in Section 4.4. (ARR after IPN)
- AF of greater than 6 minutes, 1 hour, 6 hours, and 24 hours duration detected on ambulatory ECG monitoring following an irregular pulse watch notification. (AFtime after IPN)
- Self-reported initiation of therapies for AF, including anticoagulant, rate-controlling and anti-arrhythmic therapy. (therapies)

- Self-reported electrical or chemical cardioversion by a health care provider. (cardioversion)

3. ANALYSIS SETS

The Full Analysis Set (FAS) will consist of all participants who are enrolled in the study.

The Notification Analysis Set (NAS) will consist of all participants who receive a IPNA. This analysis set is equivalent to the Notification Subgroup. The co-primary AF endpoint will be collected from these participants to evaluate Objective 1.

The ECG Analysis Set (EAS) will consist of all participants who receive an ambulatory ECG monitor, wear it for a minimum amount of time providing a minimum analyzable time of 1 hour, self-report no history of AF prior to the time of consent, and who were not associated with a technical issue arising from the AHS app preventing linkage of the patch data with the tachogram data. The identification of the subjects to be removed from the EAS will be finalized prior to data analysis. This analysis set includes all participants in the ambulatory ECG monitor subgroup who wear their patch providing at least 1 hour of analyzable time. The co-primary tachogram endpoint will be collected from these participants to evaluate Objective 2. All tachogram- and alert-level outcomes will be estimated from this analysis set during times when tachograms are being recorded by Apple Watch during simultaneous, analyzable ECG monitoring. The ambulatory ECG monitor recordings will be measured during the entire period the patch is worn.

Analyses performed at the tachogram level will further restrict the EAS to participants who began wearing their patch within 14 days of shipment.

Table 1 Analysis Sets and the Unit of Analysis to be Used for Each Endpoint

Endpoint	Analysis set	Unit of analysis	Concurrent
AF after IPN [primary]	EAS	participant	not concurrent
ePatch+ [primary]	EAS	tachogram	concurrent
IPNA+ [secondary]	EAS	participant	concurrent
PCP PRO after IPN [secondary]	NAS	participant	not concurrent
ARR after IPN [tertiary]	EAS	participant	not concurrent

AFtime after IPN [tertiary]	EAS	participant	not concurrent
Therapies [tertiary]	NAS, FAS	participant	not concurrent
Cardioversion [tertiary]	NAS, FAS	participant	not concurrent

Note: The concurrent column indicates whether the estimate is based on measures recorded simultaneously.

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 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 summarised 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 and overall, for the NAS and FAS.

	NAS	FAS
22-39 N Completed the study #,% Discontinued from study #,% Reasons for discontinuation		
40-54 N Completed the study #,% Discontinued from study #,% Reasons for discontinuation		
55-64 N Completed the study #,% Discontinued from study #,% Reasons for discontinuation		

65+ N Completed the study #,% Discontinued from study #,% Reasons for discontinuation		
Overall N Completed the study #,% Discontinued from study #,% Reasons for discontinuation		

The number and percent of participants who withdrew from the study will be summarized by age group and overall, for the NAS and EAS.

	Withdrawals			
	N NAS	% NAS	N EAS	% EAS
22-39				
40-54				
55-64				
65+				
Overall				

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

	N FAS	N PDs	PDs/FAS
22-39			
40-54			
55-64			
65+			

Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by age and overall using the FAS and the EAS. No statistical test 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, overall and by treatment group (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	<40, 40-54, 55-64, >= 65 years
Gender	Categorical	Female Male Non-binary
Race	Categorical	White Hispanic, Latino, or Spanish origin Black or African American Asian American Indian or Alaska Native Middle Eastern or North African Native Hawaiian or other Pacific Islander Some other race, ethnicity, or origin Prefer not to respond
BMI	Categorical and Continuous	<30 kg/m2 and ≥30 kg/m2
Medical History	Categorical	Hypertension Diabetes mellitus Myocardial infarction Heart failure Stroke or transient ischemic attack Peripheral arterial disease
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

Medications

Medications reported during study visit 1 will be summarized using the FAS by drug category or generic drug name by age group.

Drug Category or Name	N Responding	% Responding (of FAS)	% Responding (of NAS)	N on Medication(%)*
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 Co-primary Endpoint Addressing Objective 1

We have designed the study to estimate the proportion of participants age 65 or older diagnosed with AF within a 0.10 confidence interval width. This proportion will be estimated

as the number of participants who receive an IPN and have AF confirmed via adjudication of the ambulatory ECG monitoring divided by the number of participants who receive an IPN and who have analyzable ECG patch data. In other words, we have designed the study so the 97.5% confidence interval around the probability of AF diagnosis among those 65 and older who receive a notification will have a width of 10%. Our analysis set will be the participants 65 or older in the EAS. We will repeat the analysis to include participants of all ages in the EAS to address Objective 1b.

	N EAS	N IPN and AF diagnosis	IPN and AF diagnosis/EAS	97.5% CI
65+				

There is no hypothesis testing for the co-primary objectives. We use 97.5% confidence intervals to account for having two primary objectives.

Analysis of the Co-primary Endpoint Addressing Objective 2

We assume that each tachogram measured on a participant is independent of other intervals measured from that participant. In sensitivity analyses, we will evaluate the impact of this assumption. From the available intervals, we will sample intervals as follows:

1. Randomly sample 10 intervals per participant in the EAS to ensure each participant contributes a comparable period of data on which to evaluate concordance. We ignore whether the tachograms are positive or not in this step. All intervals will be selected in participants who have fewer than 10 intervals available.
2. Sum the number of positive tachograms sampled.
    a. Sample from the unsampled positive tachograms until that participant has 25 positive tachograms or until all positive tachograms for that participant have been sampled if that participant has less than 25 positive tachograms.
3. Sample 1 silent IPN per participant that contains the full series of >= 5 tachograms and select all tachograms corresponding to that silent IPN for adjudication.

This proportion will be estimated as the number of tachograms indicating an irregular rhythm where AF is present as confirmed via adjudication of the ambulatory ECG monitoring divided by the number of tachograms indicating an irregular rhythm sampled from the period of time when the participant provides analyzable ECG patch data.

	N Irregular tachograms	N Irregular rhythm on ECG	Irregular rhythm on ECG/ Irregular tachograms	97.5% CI
22-39				
40-54				
55-64				
65+				

Secondary and Tertiary Analyses

All secondary and tertiary endpoints will be analyzed as proportions with 95% confidence intervals. Endpoints measured using data collected from the ambulatory ECG monitoring will be analyzed in the EAS while self-reported contact with a health care provider and initiation of therapies or cardioversion will be analyzed in the NAS. The self-reported outcomes (90-day after notification of pulse irregularity and end of study PROs) will also be analyzed in the NAS and FAS, respectively. Generalized linear regression techniques will be employed to evaluate the variation observed in secondary and tertiary endpoints by subgroups described by age, race, gender, and family history.

- Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with AF of greater than 30 seconds duration when the IPNA based on multiple tachograms is positive for an irregular pulse among those who received a notification. These positive IPNA triggers will not result in additional notifications to participant, but will be available for analyses. Each participant contributes one observation. (IPNA+)

	N EAS	N IPNA+	Irregular tachogram on ECG (within the alert timeframe)	Irregular tachogram on ECG (within the alert timeframe)/IPNA+	95% CI
22-39					
40-54					

55-64					
65+					

- Self-reported contact with a health care provider within 3 months following an irregular pulse notification. (PCP PRO after IPN)

	N NAS	N Self-reported contact	Self-reported contact/NAS	95% CI
22-39				
40-54				
55-64				
65+				

-

4.4 Tertiary Endpoints

- An indicator for the presence of arrhythmias other than AF detected on ambulatory ECG monitoring that can also result in an irregular pulse. Arrhythmias considered include sinus arrhythmia, frequent premature atrial contractions (PAC), frequent premature ventricular contractions (PVC), intermittent heart block, multifocal atrial tachycardia, and atrial tachycardia with variable conduction. Definitions of each arrhythmia are provided in Section 4.4. (ARR after IPN)

	N EAS	N ARR on ECG	N Alerts	Alert/ARR on ECG	95% CI
65+					

- AF of greater than 6 minutes, 1 hour, 6 hours, and 24 hours duration detected on ambulatory ECG monitoring following an irregular pulse watch notification. (AFtime after IPN)

- Self-reported initiation of therapies for AF, including anticoagulant, rate-controlling and anti-arrhythmic therapy. (therapies)
- Self-reported electrical or chemical cardioversion by a health care provider. (cardioversion)

Sensitivity and Sub-analyses

As a sensitivity analysis, a per-protocol analysis will be performed for the primary endpoints excluding participants with protocol deviations.

Proportions along with 97.5% confidence intervals will be used to analyze the co-primary objectives and will be presented separately by age (<40, 40-54, 55-64, 65+), sex, race, medical history, type of AF, and non-AF irregular rhythms. Frequency of notifications will be estimated separately by age, sex, race, and medical history in the FAS. These analyses will also be performed on participants of all ages combined.

To better understand the performance of the IPNA across the participant population, we will perform a subgroup analysis to understand the proportion estimated in Objective 1a and 1b according to the burden of AF. We will consider three approaches to split the participants into tertiles, each capturing AF burden or a related measure.

- We will split the participants into tertiles based on AF burden obtained from their ambulatory ECG monitoring.
- We will calculate each participant's PPV by calculating the proportion of their 10 sampled positive tachograms that are concordant with the ambulatory ECG monitoring and split the participants into tertiles according to the PPV calculated.
- We will split the participants into tertiles based on the time until AF appears on their ambulatory ECG monitoring.

For each approach, we will construct separate 95% confidence intervals around the probability of being diagnosed with AF in each tertile. These analyses will help us to understand how the estimates addressing Objective 1a and 1b differ according to AF burden.

We will summarize the self-reported contact with a health care provider, use of subsequent therapies for AF, and reason for not following up with a health care provider within 3 months after notification among participants who receive a notification but do not receive an ePatch.

To understand the sensitivity of our findings to the assumptions about missing data due to short wear times, we will vary the requirement that participants with less than 1 hour of wear time be considered as missing their ECG data. We will conduct additional sensitivity analyses considering the following alternative minimum wear times: 6 hours, 1 day, 2 days, and 5 days. Such analyses may provide insight into whether performance of the IPNA varies by a minimal

observational time, which may or may not have a correlation to characteristics of clinical relevance including burden of AF.

To evaluate the uncertainty introduced by sampling tachograms in the co-primary endpoint, we will perform additional analyses to understand the variability in the estimated confidence intervals across various samples. Because only sampled tachograms will be adjudicated by clinicians, we will use the results of the BioT overreads in place of the adjudicated results. We will repeat the tachogram sampling in 10,000 bootstrap resamples and calculate the confidence interval in each replicate to generate a distribution of confidence intervals based on the resamples. We will graphically display the distribution of confidence intervals and will summarize the upper and lower bounds of the confidence intervals to characterize the uncertainty in our estimated confidence intervals.

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 in the FAS and the NAS and will summarize the proportion of participants reporting rash in the NAS and EAS. AEs reported with an action taken of "Investigational product permanently stopped" will be summarized by age group and overall in participants who receive notifications, in participants who do not receive notifications, and overall. 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).

	N FAS	% FAS	N NAS	% NAS
#AEs Anxiety				
#AEs Rash				

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

	N SAEs	N unique participants with SAEs	SAEs/participants with SAEs
22-39			
40-54			
55-64			
65+			
Overall			

Analysis of Fall-Out Subgroup

The fall-out subgroup (a subset of the NAS) will include participants who received a notification, but provide incomplete data for various reasons or delay in providing data. The reasons for inclusion in the fall-out subgroup are:

- Failure to call Study Telehealth Provider within 30 days after notification.
- Urgent symptoms discovered during Study Visit #1 virtual medical evaluation by Study Telehealth Provider requiring immediate direction to EMS (urgent care clinic or emergency room) for medical care.
- Failure to return an ePatch within 45 Days after Visit #1.

We will estimate the proportion who self-report contact with a health care provider within 3 months after notification and subsequent therapies for AF in the fall-out subgroup. Furthermore, we will summarize the self-reported reasons for not following up with a health care provider in the fall-out subgroup.

Analysis to Determine Minimum Requirements for Wear Time of the ePatch

An analysis will be conducted to identify the minimum amount of wear time of the ePatch required to identify most cases of AF. For all participants positively determined to have AF

during their observation time via ePatch, we will graphically depict the time at which AF was first detected over time. In addition, for all patients with an IPN in the EAS, time to AF will be derived as a right-censored variable where the variable is equal to the minimum of the time until the first AF event or the length of time the ambulatory ECG patch is worn. Participants who do not have any AF events during their patch wear time will be right-censored at the end of their patch wear.

Our objective will be to identify the amount of wear time needed to capture 90% of AF events occurring during the 7 day wear period. To that end, we will graphically depict the AF-free curve using Kaplan-Meier methods. The time when 90% of AF events have occurred will be estimated from the curve along with a 95% confidence interval calculated using Greenwood's formula.

Device Sensitivity Analysis

We will perform an analysis to estimate the sensitivity (i.e. the true positive rate) of the device in detecting irregularities consistent with AF. In the analysis, we will estimate the proportion of participants who have an IPNA positive for an irregular rhythm consistent with AF during the period when they are undergoing simultaneous ambulatory ECG monitoring among participants with AF confirmed by ECG. These positive IPNA triggers will not result in additional notifications to participant, but will be available for analyses. Each participant contributes one observation in this analysis. We expect that the device sensitivity may be low. The low sensitivity is expected because tachograms are retrieved only when available from the Apple Watch platform; the Heart Study app does not have the ability to control the collection and storage of tachograms and relies on the platform to do this.

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.

Tachogram Level Concordance

For AF, the ambulatory ECG monitoring will be considered to be concordant with a positive tachogram if there is at least 30 seconds of AF observed on the ambulatory ECG monitor during the tachogram and the 1 minute recorded before and after the tachogram. The participant-level definition described above for sinus arrhythmia, intermittent heart block, multifocal atrial tachycardia, and atrial tachycardia with variable conduction will be applied to the period of ambulatory ECG monitoring during the tachogram and the 1 minute recorded before and after the tachogram. The 1 minute buffer is to ensure that clock drift between the Watch and ECG patch does not invalidate the “simultaneous” nature of the comparison.

For frequent PACs, the ambulatory ECG monitoring will be considered to be concordant with a positive tachogram if there are 3 or more PACs observed on the ambulatory ECG monitor during the tachogram and the 1 minute recorded before and after the tachogram. For frequent PVCs, the ambulatory ECG monitoring will be considered to be concordant with a positive tachogram if there are 3 or more PVCs observed on the ambulatory ECG monitor during the tachogram and the 1 minute recorded before and after the tachogram. Very frequent PVCs occur when 9 or more PVCs are observed.

Tachogram level concordance will only be estimated for participants who began wearing the ECG patch within 14 days of shipment so that clock drift between the Watch and ECG patch

does not exceed the 1 minute buffer described above and invalidate the "simultaneous" nature of the comparison.

Notification Level Concordance

The ambulatory ECG monitoring will be considered to be concordant with a positive IPNA if 30 seconds of AF is observed on the ambulatory ECG monitor during any of the 5-6 tachograms recorded during the period triggering the notification and the 1 minute recorded before and after each of the tachograms.

4.6 Handling of Missing Data

In analyses where the endpoint is measured using data collected from the ambulatory ECG monitoring, participants who have at least one hour of analyzable wear time during the simultaneous ECG monitoring will be included in the analyses (EAS). We will use any available tachograms and no data will be considered missing.

Multiple imputation methods will be used in the analyses of patient reported outcomes to account for an expected small proportion of participants who do not complete all questions.

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 the true AF in participants who receive an irregular pulse notification. We describe above sensitivity analyses to evaluate the sensitivity of our estimate 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 estimate of the true PPV.

- 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 IPN because the AF that triggered the initial notification may not be detected during the subsequent ambulatory ECG

monitoring. To evaluate the degree that the true proportion may be underestimated, we will compare the proportion of patients with AF as estimated in Objective 1a and 1b (the first primary endpoint below) with the proportion of concordant intervals as estimated in the first secondary endpoint. Furthermore, we will evaluate the sensitivity of our estimates addressing Primary Objectives 1 and 2 to the minimum wear time for inclusion in the analysis (described in Section 4.3).

- Missing Data Bias: For some participants, the IPN 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 Primary Objectives 1 and 2 . 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 IPN but the subsequent ECG monitoring may not be of sufficient length to observe AF. If this bias is present, we would expect to see the Kaplan-Meier plot in the analysis to determine minimum requirements for wear time of the ePatch continue to increase through the maximum wear time observed (as opposed to a Kaplan-Meier plot that plateaus prior to the maximum wear time observed).

- Spectrum Bias: Varying lengths of watch wearing across participants could lead us to identify more paroxysmal than persistent AF. In a tertiary analysis, we aim to understand the sensitivity of our findings to the definition of AF based on observing at least 60 seconds of AF. We consider AF lasting at least 6 minutes, 1 hour, 6 hours, and 24 hours as alternative definitions.

- Gold Standard Bias: It is possible that an IPN may occur during the simultaneous ambulatory ECG monitoring but the ECG incorrectly indicates no AF is present. We aim to mitigate this bias by using an FDA-cleared device and implementing a clinical adjudication process to over-read both the ePatch report and individual tachogram time-point on the raw ECG data.

Analyses performed at the tachogram level assume that the tachograms within the same participant are independent; however, this assumption may be violated because the tachograms are samples from an underlying process. We will evaluate our assumption of independence using the Wald-Wolfowitz run test to evaluate whether the sequence of positive tachograms within participants is longer than expected. If the test indicates that the

assumption may be violated (as indicated by a p-value less than 0.05), we will consider alternate methods to account for the non-independence of tachograms, including statistical methods that incorporate the correlation within a participant and a sampling approach to select tachograms that are farther apart in time and hence expected to be less correlated.

5. INTERIM CHECKS

A series of interim checks will be performed.

Throughout the course of the study, we will check the number of irregular pulse watch notifications occurring per age subgroup. If a high number of notifications is observed (greater than 10%), enrollment may be paused or throttled downward in any age subgroup (<40, 40-54, 55-64, ≥65), as informed by the empirical findings. If the number of notifications observed is less than the study infrastructure capacity, the numbers of participants invited to enroll from the "waiting period" may be increased.

	N FAS	N IPN	Alert Rate (IPN/FAS)	Greater than 10%?
<40				
40-54				
55-64				
65+				

An interim check will be performed upon completion of the first 100 ambulatory ECG monitors in each of the four age subgroups. The interim check will be performed for each subgroup regardless of how many patches are received in other age subgroups. We estimate the first check to occur at approximately 6-8 weeks after the first participant enrolled to check the following:

1) At least 50% of participants notified of an irregular pulse are ultimately wearing and returning the ambulatory ECG monitor. A low rate of ambulatory ECG monitor use would result in an increase in the rates of invitations to enrollment in any age subgroup.

2) Percentage of AF noted on ambulatory ECG monitoring is greater than 1%. A detection of AF less than 1% will prompt a cessation of enrollment in any corresponding age subgroup.

3) Percentage of non-clinically relevant irregular rhythms is greater than 90%. If the vast majority of rhythms detected on ambulatory ECG monitoring are due to other irregular, non-AF arrhythmias, such as sinus arrhythmia, frequent PACs and frequent PVCs, this will prompt a cessation of enrollment in any corresponding age subgroup.

The co-primary endpoints will be evaluated after at least 503 participants aged ≥65 have at least 1 hour of ambulatory ECG monitor data recorded, i.e. at least 503 participants who are in the EAS.

	N EAS	N IPN	N AF diagnosis	IPN and AF diagnosis/EAS (97.5% CI)	N Irregular rhythm on ECG	N Irregular tachograms	Irregular rhythm on ECG/# Irregular tachograms (97.5% CI)
22-39							
40-54							
55-64							
65+							

These analyses are designed to maintain trial integrity and patient safety and not designed to evaluate ultimate efficacy or futility and do not impact the Type I error as we will not be examining the positive predictive values of the co-primary endpoints using this interim analysis.

A much higher than anticipated rate of notifications and subsequent ePatch evaluations may result in marginal benefit of additional participant enrollment. The following will be set as maximum targets for ePatch monitoring. Exceeding these limits will trigger either a throttling downward or cessation of enrollment:

1) Completion of 5,000 ePatches in total in either participants ≥ 65 or participants aged 22-64 will result in cessation of enrollment in the corresponding age group.
2) Completion of > 100 ePatches per week in either participants ≥ 65 or participants aged 22-64 will result in a throttling downward of enrollment invitations in the corresponding age groups.

6. VALIDATION PLAN

6.1 Reproducibility Plan on Sub-Study Analysis

Stanford will follow the methods described in the AHS Sub-Study SAP (SSSAP) with the goal of reproducing Apple's results using the data collected per the AHS Sub-Study Protocol. The Sub-Study is limited to the sub-study participants as of approximately June 22, 2018. This reproducibility plan encompasses all primary and secondary endpoints described in Section 5 of the SSSAP (primary efficacy endpoint, secondary efficacy endpoint, and the primary safety endpoint).

The reproduction will include reproducing the sampling of the tachograms. Apple will provide Stanford with the seed used to generate the pseudorandom numbers used to select the sampled tachograms. Stanford will apply the seed to the data provided by Apple to check that the tachograms sampled match the sample used by Apple in the Sub-Study analysis. Apple will provide Stanford with the sampled tachograms used by Apple in the Sub-Study analysis for verification.

Next, we will compare 1) the number of tachograms classified as AF according to the spot tachogram algorithm and 2) the number of tachograms classified as AF by both the spot tachogram algorithm and the paired ECG strip is classified as AF. If both of these counts match, the PPV has been reproduced. If either count does not match, Stanford will share the list of tachograms identified as being AF by the spot tachogram algorithm and in the paired ECG strips with Apple to identify the source of the discrepancy. This process will be repeated for the secondary efficacy endpoint looking at the PPV of the alerts.

Next, a 97.5% lower confidence bound will be calculated for the primary efficacy endpoint of spot tachogram-level PPV for AF following the methods outlined in Section 9.3 of the SSSAP. If the lower bound for the spot tachogram-level PPV exceeds 70%, the null hypothesis described in the SSSAP will be rejected. For the PPV of the alerts, a two-sided exact 95% confidence interval will be computed per Section 9.3 of the SSSAP. Stanford will

compare all confidence interval bounds and the results of the hypothesis test with Apple. If any discrepancies are found, the two groups will discuss to identify the discrepancy.

Finally, the number of serious adverse device events (ADEs) and the number and percent of participants experiencing ADEs will be calculated. If any of the counts or the percent do not match, Stanford will share their list of ADEs and participants experiencing ADEs with Apple to identify the source of the discrepancy.

6.2 Replication on Final AHS Study Data

Stanford will repeat the analyses described in the reproducibility plan using the final Apple Heart Study data set. The results of the analyses will be compared with the results based on the adjudicated patches received by approximately June 22, 2018. If discrepancies are found, the results will additionally be displayed separately using data obtained before and after June 22, 2018 to demonstrate the difference between the two time periods.

The results will also be compared with the results obtained using the methods described in earlier sections of this SAP. If a discrepancy is observed here, additional investigations will be undertaken to identify the methodological source of the discrepancy between the two approaches.

A1. APPENDIX: AHS SUB-STUDY PROTOCOL AND SAP