ECG app 2.0 Algorithms Clinical Validation Study

Sponsor:	**Apple Inc.**
Protocol Number	**013**
Version and date:	**[redacted] – 5 December 2019**
Compliance Statement:	This study will be conducted in accordance with this protocol, the Declaration of Helsinki, and ICH GCP Guidelines, and the applicable regulatory requirements (21 CFR Parts 50, 54, 56, and 812). The conduct of the study will be approved by the US Food and Drug Administration (FDA) and appropriate Institutional Review Board (IRB) of the respective Investigational site. Safety assessments (adverse events) for this study will be conducted in accordance with ISO 14155-1 (2011).

[redacted]

INVESTIGATOR APPROVAL PROTOCOL SIGNATURE PAGE

Protocol:
Title: ECG app 2.0 Algorithms Clinical Validation Study

Amendment: [redacted]

I confirm that I have read and understood this trial protocol and attached appendices and will conduct this study in compliance with the protocol, all statements regarding confidentiality, local regulations, International Council for Harmonization Good Clinical Practice E6 (ICH-GCP), and United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (21 CFR Parts 50 [protection of human subjects], 54 [financial disclosure by clinical investigators], 56 [informed consent and Institutional Review Board (IRB) requirements], 812 [Investigational Device Exemptions]).

With my signature, I agree to:

(i) Conduct the investigation in accordance with the agreement, the investigational plan, applicable provisions of 21 CFR Part 812 and other Food and Drug Administration (FDA) regulations, and conditions of approval imposed by the reviewing IRB or FDA;

(ii) Supervise all testing of the device involving human subjects; and

(iii) Ensure that the requirements for obtaining informed consent are met.

Reviewed and Approved by:

[TO BE SIGNED WHEN PROTOCOL IS FINALIZED]

Investigator's Signature Date

Name/Title

SYNOPSIS

Study Title	ECG app 2.0 Algorithms Clinical Validation Study
Protocol Version	[redacted]
Protocol Date	5 December 2019
Study Design	Prospective, multi-center, non-significant risk study.
Key Inclusion Criteria	All cohorts: • Age 22 or older • Resides in the United States (US) and will remain in the US for the duration of the study • Able to read and understand a written ICF • Wrist circumference between 130 mm and 245 mm Cohort 1: No known history of atrial fibrillation (AF) and in normal sinus rhythm at the time of screening Cohort 2: Known persistent or permanent or chronic AF, and be in AF at the time of screening
Key Exclusion Criteria	All cohorts: • Physical disability that precludes safe and adequate testing • Physical or medical impairments that preclude exercise testing such as musculoskeletal back pain, arthritis, leg claudication, etc. • Mental impairment that in the opinion of the Investigator would not allow subject to complete the trial • Pregnant women at the time of the screening visit • Subjects with any Medical History, Physical exam, vital sign or any other study procedure finding/assessment that in the opinion of the investigator could compromise subject safety during study participation or interfere with the study integrity and/or the accurate assessment of the study objectives. This includes patients with known untreated medical conditions that are considered clinically significant by the Investigator, such as but not limited to significant anemia, important electrolyte imbalance and untreated or uncontrolled thyroid disease. Physical exam limitations include but

	not limited to open wound(s) on the wrist and forearm where the subject will be wearing the watch. • Vital signs measurement, medical history, or physical exam finding that makes the subject inappropriate for participation according to the Investigator • Skin conditions on either wrist that would preclude subject from wearing watch on the preferred wrist. Severe symptomatic (or active) overly dry/injured skin, skin disorders, or allergic skin reactions such as eczema, rosacea, impetigo, dermatomyositis or allergic contact dermatitis on wrist and locations where the electrodes will be placed (e.g. chest, forearms, stomach), as determined by the investigator. • Known allergy or significant sensitivity to medical adhesives, isopropyl alcohol, or ECG patch • Known allergy or sensitivity to fluorocarbon-based synthetic rubber, such as fluoroelastomer bands primarily used in the wrist worn fitness devices • Clinically significant hand tremors as judged by the Investigator • [redacted] • Subjects with implanted cardiac devices such as a Pacemaker or an automated Implantable Cardioverter - Defibrillator
Study Objective	The objective of this study is to evaluate the performance of the investigational ECG app 2.0 algorithms.

Endpoints	**Co-Primary Endpoints:** 1a. Correct classification of subjects with normal sinus rhythm (HR 50-150) on simultaneous 12-lead ECG as "Sinus Rhythm" or "High Heart rate" on a readable and classifiable ECG app strip. [Specificity] 1b. Correct classification of subjects with AF (HR 50-150) on simultaneous 12-lead ECG as "AF" on a readable and classifiable ECG app strip. [Sensitivity] **Secondary Endpoints:** 2a. Correct classification of subjects with normal sinus rhythm (HR 50-99, sinus rhythm (SR) on simultaneous 12-lead ECG) as "Sinus Rhythm" on a readable and classifiable ECG app strip 2b. Correct classification of subjects with AF (HR 50-99, AF on simultaneous 12-lead ECG) as "AF" on a readable and classifiable ECG app strip 2c. Correct classification of subjects with sinus tachycardia (HR 100-150, SR on simultaneous 12-lead ECG) as "High Heart Rate" on a readable and classifiable ECG app strip 2d. Correct classification of subjects with AF with high heart rate (HR 100-150, AF on simultaneous 12-lead ECG) as "AF (high heart rate)" on a readable and classifiable ECG app strip 2e. Equivalence of the ECG app waveform to Lead I from a 12-lead ECG as measured by acceptable morphology of PQRST complexes 2f. Equivalence of the ECG app waveform to Lead I from a 12-lead ECG as measured by R-Wave amplitude agreement
Test Device	Investigational ECG app 2.0 algorithms
Study App	ECG App for Data Collection
Reference Device	12-lead ECG (GE Healthcare Cardiosoft Systems (K031561))
Study Procedures	Subjects will wear an Apple Watch and record a single lead ECG using the ECG sensor on Apple Watch and a simultaneous 12-lead ECG. Subjects will exercise to target a HR of at least 85% of predicted max heart rate (not to exceed 150 bpm), then record a 30- second single lead ECG using the ECG sensor on Apple Watch and a simultaneous 12-lead ECG. After data collection, the investigational ECG app

	algorithms will be run on the sensor data collected from subjects to generate waveforms and rhythm classifications. 12-lead ECGs will be adjudicated for rhythm diagnosis by 2 independent US Board Certified Cardiologists (with a 3rd reviewer in the event of discrepancy). Waveform comparison will be adjudicated by 2 independent cardiac technicians (with a 3rd reviewer in the event of discrepancy).
Duration of Study Participation	Approximately 4 hours
Total Number of Study Subjects Enrolled	Approximately 568 subjects total, including approximately 168 with sinus rhythm and approximately 400 with AF.

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LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation	Explanation
ADE	Adverse device effect
AE	Adverse event
AF	Atrial fibrillation
AFL	Atrial flutter
BMI	Body mass index
CFR	Code of Federal Regulations
CRO	Contract research organization
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council for Harmonization
IRB	Institutional Review Board
NA	Not applicable
PAF	Paroxysmal atrial fibrillation
QC	Quality control
SADE	Serious adverse device effect
SAE	Serious adverse event
SR	Sinus rhythm
SVT	Supraventricular tachycardia
UADE	Unexpected adverse device effect
US	United States

1. INTRODUCTION

1.1. Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and when left untreated, is a leading cause of morbidity and mortality from stroke, heart failure and myocardial infarction[i,ii]. Data from the Framingham Heart Study indicates that by age 40 years, lifetime risk for developing AF is 1 in 4[iii]. AF is also a growing public health problem with prevalence projected to triple between 2010 and 2050, with an estimated 12.1 million diagnosed cases in 2030 in the United States (US) alone[iv].

Early detection and treatment of patients with AF minimizes the risk of sequelae of thromboembolism including >60% reduced risk of stroke[ii,v]. However, atrial fibrillation is commonly underdiagnosed; many people with AF are asymptomatic or experience mild nonspecific symptoms for which they do not seek medical attention or screening.[ii]. As a result, asymptomatic patients are 3 times as likely to have sustained an ischemic stroke prior to diagnosis than those with symptoms[i,vi]. These findings raise concerns and have prompted several variations of screening programs to detect patients with asymptomatic AF to prevent an embolic event[i,ii]. While systematic and opportunistic screening programs have demonstrated increased rates of detection when compared to detection during routine clinical practice, such screening programs are not yet widely implemented[ii]. Additionally, AF may be paroxysmal (PAF or intermittent AF) and therefore missed by recording a single in-clinic electrocardiogram (ECG). This is especially true for those patients with intermittent symptoms. Holter devices are commonly used for ambulatory 24-hour ECG monitoring in at-risk patients, but have limited sensitivity for the detection of new AF[vii]. Given that mobile ECG devices permit an on-demand assessment by a user, our hypothesis is that use of the ECG app on Apple Watch can facilitate identification of AF.

1.2. Device Description

The ECG app software is comprised of a pair of mobile medical apps—one on Apple Watch and the other on the iPhone.

The ECG Watch app analyzes data collected by the integrated electrical sensors on a compatible Apple Watch to generate an ECG waveform similar to a Lead I, calculate average heart rate, and provide a rhythm classification to the user for a given 30 second session. When a user opens the ECG Watch app while wearing the Watch on one wrist and places the finger of the opposite hand on the digital crown, they are completing the circuit across the heart which begins a recording session.

Once the recording session is complete, the ECG Watch app performs signal processing, feature extraction and rhythm classification to generate a session result.

1.3. Study Rationale

This clinical study is being conducted to support investigational ECG app 2.0 algorithms (test device) for the Apple ECG app which expand the classification heart range, introduce new classification results, and introduce minor, non-user-facing algorithm updates, and evaluate the performance of the test device.

1.4. Risk/Benefit Assessment

No significant risks or permanent side effects are anticipated. However, subjects may experience temporary discomforts or have risks while or as a result of participating in this study.

- Subjects may experience slight to moderate discomfort associated with attachment and removal of adhesive electrodes used for ECGs. The risk will be minimized by using medical-grade disposable electrodes and by leaving them attached to the skin only for the limited study duration. Even with these precautions, temporary skin irritation may still occur.
- Subjects may experience slight to moderate discomfort associated with wearing the Apple Watch.
- Exercising on a treadmill or stationary bike may cause temporary discomfort due to exertion. This risk will be minimized by asking subjects to self-select exercise intensity, so subjects may choose to reduce the workload at any time if necessary.
- Subjects participating in exercise may feel other symptoms, including but not limited to dizziness, heart palpitations, anxiety, and shortness of breath.
- Rarely, people with atrial fibrillation (AF) may experience an abnormal heart rhythm that may be life-threatening and/or require further treatment. If this happens, subject participation in the study may be terminated.

2. STUDY OBJECTIVES, ENDPOINTS, AND HYPOTHESES

2.1. Study Objective

The objective of this study is to evaluate the performance of the Test Device.

2.2. Study Endpoints

Co-Primary Endpoints:

1a. Correct classification of subjects with normal sinus rhythm (HR 50-150) on simultaneous 12-lead ECG as "Sinus Rhythm" or "High Heart rate" on a readable and classifiable ECG app strip. [Specificity]

1b. Correct classification of subjects with AF (HR 50-150) on simultaneous 12-lead ECG as "AF" on a readable and classifiable ECG app strip. [Sensitivity]

Secondary Endpoints:

2a. Correct classification of subjects with normal sinus rhythm (HR 50-99, sinus rhythm (SR) on simultaneous 12-lead ECG) as "Sinus Rhythm" on a readable and classifiable ECG app strip

2b. Correct classification of subjects with AF (HR 50-99, AF on simultaneous 12-lead ECG) as "AF" on a readable and classifiable ECG app strip

2c. Correct classification of subjects with sinus tachycardia (HR 100-150, SR on simultaneous 12-lead ECG) as "High Heart Rate" on a readable and classifiable ECG app strip

2d. Correct classification of subjects with AF with high heart rate (HR 100-150, AF on simultaneous 12-lead ECG) as "AF (high heart rate)" on a readable and classifiable ECG app strip

2e. Equivalence of the ECG app waveform to Lead I from a 12-lead ECG as measured by acceptable morphology of PQRST complexes

2f. Equivalence of the ECG app waveform to Lead I from a 12-lead ECG as measured by R-Wave amplitude agreement

2.3. Study Hypotheses

[redacted]

[redacted]

[redacted]

3. STUDY DESIGN

3.1. Overview

This is a prospective, non-significant risk study. The study protocol will undergo review and approval by an Institutional Review Board (IRB) prior to enrolling study subjects.

Written, informed consent will be obtained from all subjects before any protocol-directed procedures are performed. All potential subjects will participate in a screening visit, and if eligibility is confirmed, subjects may begin study participation at the same visit.

The investigational ECG app 2.0 algorithms (test device) will be run post-hoc on the sensor dataset to generate ECG app waveforms and classifications. The performance of the test device will be determined based upon adjudication of concurrent data from the reference device.

3.2. Required Equipment

3.2.1. Sponsor-Provided

The Sponsor will provide the study sites with sufficient Apple Watch Series 4 and 5 to complete the study. iPhones will also be provided to study sites, but subjects will not be expected to interact with these iPhones (for clinical research staff to upload data to study sponsor only). Sponsor will provide 12-lead ECG monitor: GE Healthcare CardioSoft Systems. CardioSoft is an FDA cleared ECG device (K031561). All study equipment will be returned to the Sponsor at the end of the study. All study equipment will be pre-labelled and supplied to the Investigational Site by Sponsor.

No specific packaging of the study equipment is required, as this study is non-interventional and will temporarily dispense study equipment to subjects.

3.2.2. Storage and Handling Procedure

All study equipment and reference devices (the “study equipment”) will be stored in normal room temperature/humidity/pressure conditions with no exposure to direct sunlight or heat source throughout the study. The storage area should be secure with restricted access.

3.2.3. Accountability

Test and reference device ID numbers used for each subject will be recorded in the source documents. All study equipment will be returned to the Sponsor at the end of the study.

3.2.4. Investigational Study Site-Provided

- Space to screen subjects
- Space to conduct testing and regular examination room/office equipment
- Treadmill
- Stationary bike
- Equipment to record vital signs
- Appropriate safe and storage area for study equipment

3.3. Qualification Criteria for US Board-Certified Cardiologists

Reviewers of 12-lead ECG data must be US board-certified medical doctors specialized in cardiology.

Reviewers of ECG waveforms will be Certified Cardiographic Technicians.

Curriculum vitae and medical license will be collected for each US board-certified medical doctors specialized in cardiology.

3.4. Randomization and Blinding

Subjects in this study will not be randomized to any treatment regimens.

Approximately 100 subjects (50 SR; 50 AF) will be randomly selected to assess waveform equivalence of the ECG app to Lead 1 from a 12-Lead ECG. Subjects will be randomly selected using a systematic sampling approach. A number between 1 and 6 will be randomly selected for the AF cohort and then every 6th consecutively enrolled AF subject will be selected at random within each site. Likewise, a number between 1 and 3 will be randomly selected for the SR cohort and then every 3rd consecutively enrolled SR subject will be selected at random within each site.

US board-certified cardiologists will be blinded to the subjects' past medical history, stage (resting or exercise) and ECG app classifications during the assessment and adjudication of ECG data.

Cardiac technicians will be blinded to the subjects' past medical history, ECG app classifications, stage (resting or exercise) and origin (ECG app or 12-lead ECG) of the waveform being reviewed during the assessment and adjudication of ECG data.

Adjudicators will be instructed to review ECGs independently and separately of each other and not to confer about diagnoses.

3.5. Duration of Subject Participation

Subjects will participate in a screening visit and, if eligible, participate in the study for 1 day (study procedures will last approximately 4 hours) within a window of 30 days after screening visit.

4. STUDY POPULATION

4.1. Subject Recruitment

Subject recruitment can be accomplished in any appropriate fashion, within the guidelines of the IRB and the investigational site(s). Recruitment will continue until enrollment requirements are met, including reaching the targeted number of subjects completing the study procedure.

Investigators should keep a record, i.e. subjects screening log, of subjects who are entered into the study. Each subject must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of screening and study participation. The sponsor must approve any changes to the target distribution of subjects in writing prior to enrollment.

4.2. Study Cohorts and Target Population

The study will include two cohorts of subjects:

- Cohort 1 will include subjects with no known history of AF and are in normal sinus rhythm at time of screening
- Cohort 2 will include subjects with known persistent or permanent or chronic AF who are in AF at the time of screening

The following age, gender, and race/ethnicity enrollment targets will be adhered to during subject recruitment:

- A minimum of 20% of subjects in both cohorts will be enrolled in each of the age categories of 55 to 64, and ≥65 years, and a minimum of 10% of subjects in both cohorts in the age category of <55 years..
- At least 40% of subjects in Cohort 1 will be female. At least 20% of subjects in Cohort 2 will be female.
- At least 30% of subjects in Cohort 1 will be either American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander.
- In Cohort 2, at least 15% of subjects will be either American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander

The incidence of AF is known to increase with age, male gender, and White race[viii]. These recruitment targets are also consistent with the subject population observed in the Apple Heart Study[ix,] which is representative of the intended use population.

4.3. Inclusion Criteria

Subjects must meet all the following inclusion criteria to be enrolled:

1. Able to read, understand, and provide written informed consent
2. Willing and able to participate in the study procedures as described in the consent form
3. Individuals who are 22 years of age and older at time of screening

4. Able to communicate effectively with and follow instructions from the study staff
5. Have a wrist circumference between 130 mm and 245 mm (Measured at "band center" on the preferred wrist).

6. Subjects enrolled into Cohort 1 must have no known medical history of AF and in normal sinus rhythm at the time of screening.
7. Subjects enrolled into Cohort 2 must have a known diagnosis of persistent or permanent or chronic AF and be in AF at the time of screening.

4.4. Exclusion Criteria

Subjects must meet none of the following criteria to be enrolled:

1. Physical disability that precludes safe and adequate testing
2. Physical or medical impairments that preclude exercise testing such as musculoskeletal back pain, arthritis, leg claudication, etc.
3. Mental impairment as determined by the Investigator
4. Pregnant women at the time of the screening visit.
5. Subjects with any Medical History, Physical exam, vital sign or any other study procedure finding/assessment that in the opinion of the investigator could compromise subject safety during study participation or interfere with the study integrity and/or the accurate assessment of the study objectives. This includes patients with known untreated medical conditions that are considered clinically significant by the Investigator, such as but not limited to significant anemia, important electrolyte imbalance and untreated or uncontrolled thyroid disease. Physical exam limitations include but not limited to open wound(s) on the wrist and forearm where the subject will be wearing the watch.
6. Any history of wrist surgery with scarring in the area of the sensor location on the wrist where the subject will be wearing the watch
7. Vital signs measurement, medical history, or physical exam finding that makes the subject inappropriate for participation according to the Investigator.
8. Tattoos or moles in the area of the sensor location on the wrist where the subject will be wearing the watch.
9. Skin conditions on either wrist that would preclude subject from wearing watch on either wrist. Severe symptomatic (or active) overly dry/injured skin, skin disorders, or allergic skin reactions such as eczema, rosacea, impetigo, dermatomyositis or allergic contact dermatitis on wrist and locations where the electrodes will be placed (e.g. chest, forearms, stomach), as determined by the investigator.
10. Known allergy or significant sensitivity to medical adhesives, isopropyl alcohol, or ECG patch

11. Known allergy or sensitivity to fluorocarbon-based synthetic rubber, such as fluoroelastomer bands primarily used in the wrist worn fitness devices.
12. Clinically significant hand tremors as judged by the Investigator.

[redacted]

14. Subjects with implantable pacemaker devices or an automated Implantable Cardioverter – Defibrillator devices

4.5. Subject Discontinuation and Replacement

Each enrolled subject shall remain in the study until completion. However, subject participating in the study is voluntary and the subject has the right to withdraw at any time. Some example of possible subject discontinuation may be:

- Subject Death
- Subject voluntary withdrawal
- Subject withdrawal by an investigator
- Subject early termination by Sponsor

The sponsor must be notified of the reason(s) for subject discontinuation. The site will provide the information to the Sponsor. Site Investigators must also report this to their respective IRB as defined per their IRB procedures.

Subject Replacement:

Subjects who discontinued from the study will be replaced as determined by Sponsor.

4.6. Subject Follow-up

No subject follow-up will be performed.

5. STUDY PROCEDURES

5.1. Screening

Informed consent will be obtained before any study protocol-directed procedures are performed. After the signing of informed consent, the subject will be evaluated for eligibility according to the study inclusion/exclusion criteria (Section 4.3 and Section 4.4).

During screening, the following should be obtained on each subject:

- Age
- Gender
- Race and ethnicity
- Diagnosed medical conditions such as: past surgical history, illness, previous diagnoses
- Prior and Concomitant Medications
- Allergies
- Tobacco and Nicotine history
- Alcohol use (self-reported)
- Recreational drug use (self-reported)
- Physical examination (will include at a minimum general appearance, lungs, chest, heart, head and neck, abdomen, musculoskeletal/extremities, lymph nodes, skin and neurological assessment)
- Height and weight
- Body mass index (BMI)
- Vital signs will be collected after sitting for at least 5 minutes. Vital signs collected may include blood pressure, heart rate, and body temperature
- Urine pregnancy testing for women of childbearing potential
- Caffeine intake
- Exercise habits
- Dominant hand
- Wrist circumference of wrist wearing the Watch
- Skin fold thickness of wrist wearing the Watch
- Wrist hairiness of wrist wearing the Watch
- Assessment of tattoos, moles, scars on wrist of wrist wearing the Watch
- 12-lead ECG will be collected supine after lying for at least 5 minutes

* For women of child-bearing potential only. A woman will be considered not of child-bearing potential if they are surgically sterile and have provided documentation, or they are ≥55 and have not had a cycle for ≥2 years.

All subjects will undergo a 12-lead ECG. The 12-lead ECG will be reviewed and interpreted by the investigator. If subjects were not previously aware of any abnormal findings on ECG, the investigator will inform the subject of the findings; any further medical care will be at the discretion of the subject's non-study medical provider. Non-AF subjects must be in normal sinus rhythm at the time of the 12-lead ECG at screening in order to be assigned to Cohort 1. AF subjects must be in AF at the time of the 12-lead ECG at screening in order to be assigned to Cohort 2. AF subjects that do not present AF at time of screening may come back another day within 7 days to determine their eligibility for Cohort 2 at a maximum of one repeat time.

If any of the study staff believe the vital signs or screening 12-lead ECG are of poor quality, they may repeat the measurements.

5.2. Study Day 1

Subjects will report to the clinic for the Day 1 visit at their scheduled date and time. No special preparation for this visit is required. If eligibility is confirmed after completion of all screening procedures, subjects may begin study participation following the screening.

Subjects will be asked to remove jewelry and any underwire bras during 12-lead ECG data collection. NOTE: Non-underwire bras are acceptable during data collection

5.2.1. Study Procedures

5.2.1.1. Data Collection Study Equipment Set up

The following procedures will be performed for each study subject at study participation:

Assign an Apple Watch and the paired iPhone to each subject and document the Apple Watch and paired iPhone numbers and the version of Study App. The Watch configurations were selected at random from the total set of Watch configurations. The random assignment of watches to subjects is based on a pre-determined randomization schedule stratified by site, age group and cohort

1. Instruct the subject to choose his/her preferred wrist to wear the Apple Watch. The Apple Watch can be worn on whichever side the subject prefers unless there is a skin condition on one wrist as noted above in the exclusion criteria, in which case, the Apple Watch must be worn on the non-affected wrist. Record the chosen wrist. If the subject does not have a side preference or skin condition on one wrist, the device will be placed on the left wrist.
2. The subject will be asked to put the Apple Watch on his/her wrist (as indicated in 1). The Apple Watch should be fitted tightly enough that it does not move when the hand/wrist is shaken.
3. Check band tightness for a snug fit and adjust as needed.

4. Instruct the subject to read the provided instructions on how to Take an ECG. Instructions will come from the "How to Take an ECG" onboarding screen of the ECG app (DEN180044) on iPhone.
5. Ask the subject to take a practice ECG. After the first practice, site study staff will guide subject to appropriate study posture and grip (if not achieved independently during the first test run).
6. Allow subject up to three additional practice sessions if more practice is needed to ensure study posture and grip instruction understanding (fewer than 3 additional practice sessions are acceptable if study posture and grip are correct and patient is comfortable with the positioning).

5.2.1.2. Data Collection – Rest ECG

1. Instruct subject to remain seated for a 5-minute resting period prior to collecting a 12-lead ECG and set the reference system to 40 Hz filter. Use standard placement of all 12-lead electrodes (with limb lead for Lead 1).
2. Collect a 12-lead ECG (review to ensure there is no artifact). The recording will be approximately 30 seconds in duration. Simultaneously, instruct the subject to record a separate complete single-lead ECG using the Apple Watch. Both data streams will be synced together by the Study Staff through a flash sync method.
    a) Monitor the 12-lead ECG to ensure a good quality recording is obtained.
    b) A total of three trials consisting of simultaneously recorded 12-lead ECG and single-lead ECG using the Apple Watch will be performed for each subject.
    c) The first trial will be used for adjudication and analysis.

    [redacted]

    d) The baseline resting heart rate for exercise (5.2.1.3) will be determined from the reference device on the 1st resting trial.

5.2.1.3. Exercise

For the exercise sessions, a target HR will be defined as 85% of predicted max HR (PMHR = 220 – age) which is not to exceed 150 bpm; thus the maximum target HR in any subject is 150 bpm. Subjects who have been cleared and deemed fit by the Investigator to exercise using the treadmill or stationary bike will complete training on how to use the exercise equipment and perform a practice session to determine adequate resistance for increasing the HR to > target HR. There will be up to 3 total exercise trials. Each trial consists of up to 5 minutes of exercise, depending on how long it takes for the target BPM of >target HR to be achieved, followed by an approximately 1 minute data capture session where the subject is stationary to complete a data capture session. Subject should be at target HR for at least 5 seconds prior to starting data collection. At the discretion of the investigator, blood pressure reading may be taken for safety purposes. During the exercise, the subject will be encouraged by the Study Staff to increase effort if the subject's initially chosen exercise intensity is too low to raise their HR by the

requisite amount. For treadmill exercise, the subject is recommended to move off the treadmill and into a seated position, then supporting their arms and elbows on their lap while completing data collection with the Apple Watch. For stationary bikes, the subject can remain on the bike and place their hands on the bike handles in a still position for data collection with the Apple Watch.

The subject may rest in between each trial for approximately 3 minutes. The subject will be monitored throughout the session. The reference ECG will be continuously monitored during the exercise session by the Investigator and/or Study Staff.

The first trial will be used for adjudication and analysis. [redacted]

5.2.2. Apple Watch Data Processing

Apple Watches will be collected, data will be transferred from the Watches to the paired iPhones by CRO staff, and data will be transferred to study sponsor.

Procedures for ECG waveform generation and ECG app classification based on the collected Apple Watch sensor data are described in Section 6.1.

5.2.3. Adjudication of ECG Data

5.2.3.1. 12-lead ECG

Thirty second 12-lead ECGs will be reviewed by 2 independent US Board Certified Cardiologist adjudicators for heart rate and rhythm. In the event of discrepancy, ECGs will be reviewed by a third adjudicator. All adjudicators will be blinded to cohort, stage (resting or exercise) and ECG app classification. Adjudicators will be instructed to review ECGs independently and separately of each other and not to confer about diagnoses. The 12-lead ECGs generated from the first trial at rest and the first trial after exercise will be adjudicated for each subject. Adjudication is based on the 30 sec of reference data, simultaneous to the watch ECG.

5.2.3.1.1. Heart Rate

Heart rate will be calculated for each 12-lead. Record the heart rate and select the heart rate diagnostic code that corresponds to the heart rate observed on the reference ECG.

5.2.3.1.2. Rhythm Diagnoses

The following rhythm diagnoses will be adjudicated to the 12-lead ECG data (Section **Error! Reference source not found.**) for each 12-lead ECG:

1. Sinus Rhythm (will include sinus bradycardia, normal sinus rhythm, and sinus tachycardia)
2. Atrial Fibrillation
3. Supraventricular tachycardia (SVT) with regular beat-to-beat intervals (e.g., AVNRT, AVRT, Atrial Tachycardia with HR over 100 beats per minute)
4. Other Abnormal Rhythm
    a. Frequent Premature Atrial Contractions (>3 in 30 seconds)
    b. Frequent Premature Ventricular Contractions (>3 in 30 seconds)
    c. Atrial flutter
    d. Ventricular tachycardia
    e. Ventricular fibrillation
    f. Second degree AV block, Type I
    g. Second degree AV block, Type II
    h. Third degree AV block
    i. Other
5. Uninterpretable

5.2.3.1.3. Combining Heart Rate and Rhythm Diagnoses on 12-lead ECG

Heart Rate	**Rhythm on 12-lead ECG**				
	Sinus Rhythm	Atrial Fibrillation	SVT with regular intervals	Other	Uninterpretable
<50	HR<50	HR<50	N/A	HR<50	Uninterpretable
50-99	SR 50-99	AF 50-99	N/A	Other 50-99	Uninterpretable
100-150	SR 100-150	AF 100-150	SVT 100-150	Other 100-150	Uninterpretable
>150	HR>150	HR>150	HR>150	HR>150	Uninterpretable

5.2.3.2. ECG Strip Overlay

1. Strip preparation

a. The Sponsor will prepare one paired set of rest ECG strips and one paired set of exercise ECG strips from 100 randomly selected subjects (50 AF; 50 SR). Each set of rest and exercise ECG strips will be comprised of the Apple Watch ECG and lead 1 ECG from the 12-lead.

2. Cardiac Core Lab review:
    a. Three blinded, independent cardiac technicians or cardiologists will review each paired sets of strips on 25mm/s, 10 mm/mV standard.
    b. One reviewer will identify the first six consecutive distinct readable PQRST complexes without artifact that match between the subject device strip and reference device strip for evaluation. For example, if the reference strip has an artifact in beats 2 and 5 but all other beats are good and the strip from the test device has artifact in beats 1 and 6 but all other beats are good, the six consecutive beats to be used will begin at beat 7 of both strips. The strips will be excluded if six consecutive beats cannot be found. The six PQRST complexes identified by the initial reviewer will be used by the 2 other reviewers.
    c. The strips will be rendered semi-transparent through the use of back lighting and overlaid to visually assess for morphological similarity.
    d. Each reviewer will assign a pass/fail to the strips by visually assessing all 6 PQRST complexes. A “pass” is given when the morphology of the PQRST complexes appears to overlay to the unaided eye.
    e. Measure R amplitude from the isoelectric baseline of the PR segment at the onset of the QRS complex to the highest vertical deflection of the R-wave. Measure to the nearest 0.5 millimeter for the first QRS complex of the six consecutive distinct readable PQRST complexes in both the reference strip and test device strip. The reviewers will be blinded to the identity of the reference strip and test device strip.

6. STATISTICAL ANALYSIS

All analyses will be performed with SAS v9.4 or higher and R (bootstrap sampling).

6.1. Dataset Generation

A single sensor dataset to generate ECG app waveforms and classifications will be used for this study to which the test device algorithm will be applied in a post-hoc fashion.

6.2. Statistical Methodology

6.2.1. Primary Endpoint Analysis

The following truth table will be generated to cross-classify data collected from enrolled subjects according to the ECG app device and adjudicated ECG data from the 12-lead ECG for the primary endpoint analyses as presented below. The rhythm classification and the heart rate will be adjudicated separately. The final adjudicated rhythm classification result will be used if there is a rhythm classification discrepancy (including the specify type of Other Abnormal Rhythm) between the first two cardiologists. The final adjudicated heart rate result will be used if there is a heart rate discrepancy between the first two cardiologists.

Table 1: Cross-classification truth table for primary endpoint analyses

Algorithm Classification	**Reference Strip Final Adjudicated Result (via 3 US Board Certified Cardiologists)**			
	SR ($50 \leq HR \leq 150$)	AF ($50 \leq HR \leq 150$)	Other (SVT or Other with HR 50-150; HR<50; HR>150)	Uninterpretable
SR (SR (50-100) + High HR no AF (101-150))	**n11**	**n12**	n13	n14
AF ($50 \leq HR \leq 150$)	**n21**	**n22**	n23	n24
Inconclusive (including HR< 50; HR>150)	n31	n32	n33	n34
Poor Recording	n41	n42	n43	n44

Note: Bold indicates data values used for the primary endpoint analyses.

The following primary endpoint hypothesis will be tested using a one-sided type I error of 0.025:

[redacted]

Using the cross-classified data from Table 1, the sensitivity and specificity for the primary endpoint hypothesis will be estimated as follows:

Sensitivity estimate = n22/(n12 + n22)

Specificity estimate = n11/(n11 + n21)

Each subject may contribute up to 2 paired ECG app and Adjudicated 12-Lead ECG results for analysis; one at rest (first trial run) and the other after exercise (first trial run).

Because data will be collected from the same subjects at rest and after exercise, a bootstrap approach will be implemented to obtain two-sided 95% confidence intervals for the sensitivity and specificity to account for potential within-subject correlation. Subjects with at least one adjudicated result of AF (for sensitivity), SR (for specificity) and with a classifiable algorithm result (i.e., SR or AF) will be selected at random with replacement and the 2.5^{th} and 97.5^{th} percentiles of the distribution of bootstrap estimates will represent the two-sided 95% confidence bounds. If the lower confidence bounds for both sensitivity and specificity exceeds the pre-established performance goal associated with these performance metrics, the null hypothesis will be rejected in favor of the alternative hypothesis.

As an additional analysis associated with the primary endpoint, the sensitivity and specificity will also be estimated and reported along with their corresponding bootstrap two-sided 95% confidence intervals by including the Inconclusive algorithm classification category in the calculation. More specifically, the sensitivity and specificity for the additional analysis will be estimated as follows:

Sensitivity estimate (additional analysis) = n22/(n12 + n22+n32)

Specificity estimate (additional analysis) = n11/(n11 + n21+n31)

6.2.2. Secondary Endpoint Analyses

The following truth table will be generated to cross-classify data collected from enrolled subjects according to the ECG app device and adjudicated ECG data from the 12-lead ECG for secondary endpoint analyses as presented below

Table 2: Cross-classification truth table for secondary endpoint analyses

	Ground Truth via Adjudicated 12-lead ECG									
	HR	*<50*	**50-99**	**50-99**	**100-150**	**100-150**	*>150*	50-150		

ECG app Device Output / Rhythm	Any	**SR**	**AF**	**SR**	**AF**	Any	SVT or Other	Uninterpretable	Total
Low HR (<50)	n11	n12	n13	n14	n15	n16	n17	n18	N1D
SR (50-99)	n21	**n22**	**n23**	**n24**	**n25**	n26	n27	n28	N2D
AF (50-99)	n31	**n32**	**n33**	**n34**	**n35**	n36	n37	n38	N3D
High HR (100-150) with no AF	n41	**n42**	**n43**	**n44**	**n45**	n46	n47	n48	N4D
AF (100-150)	n51	**n52**	**n53**	**n54**	**n55**	n56	n57	n58	N5D
HR >150	n61	n62	n63	n64	n65	n66	n67	n68	N6D
Inconclusive	n71	n72	n73	n74	n75	n76	n77	n78	N7D
Poor Recording	n81	n82	n83	n84	n85	n86	n87	n88	N8D
Total	N1	N2	N3	N4	N5	N6	N7	N8	N

Note: Bold indicates data values used for the secondary endpoint analyses.

The following four secondary endpoint hypotheses will be tested:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Using the cross-classified data from Table 2, the percent correct for each of the four secondary endpoint hypotheses will be estimated as follows:

Hypothesis 2a: Percent Correct = n22/(n22+n32+n42+n52)

Hypothesis 2b: Percent Correct = n33/(n23+n33+n43+n53)

Hypothesis 2c: Percent Correct = n44/(n24+n34+n44+n54)

Hypothesis 2d: Percent Correct = n55/(n25+n35+n45+n55)

Each subject may contribute up to 2 paired ECG app and Adjudicated 12-Lead ECG results for analysis; one will be at rest (first trial) and the other after exercise (first trial).

Because data will be collected from the same subjects at rest and after exercise, a bootstrap approach will be implemented to obtain two-sided 95% confidence intervals for the percent correct associated with each of the four secondary endpoint hypotheses to account for potential within-subject correlation. Subjects with at least one adjudicated result of SR (HR 50-99) [hypothesis 2a], AF (HR 50-99) [hypothesis 2b], SR (HR 100-150) [hypothesis 2c], AF (HR 100-150) [hypothesis 2d] and with a classifiable algorithm result will be selected at random with replacement and the 2.5^{th} and 97.5^{th} percentiles of the distribution of bootstrap estimates will represent the two-sided 95% confidence bounds. If the lower confidence bound of the percent correct equals or exceeds the pre-established performance goal associated with the associated secondary endpoint hypotheses, the null hypotheses will be rejected in favor of the alternative hypotheses.

Additional secondary endpoint analyses will be performed similarly by including the HR < 50, HR >150, and Inconclusive algorithm results in the computations of percent correct.

Two hypotheses associated with secondary objective to demonstrate that the ECG app produces a waveform that provides clinically equivalent information to Lead 1 of the 12-Lead ECG will be tested.

The first hypothesis is aimed at demonstrating that the proportion of subjects with a morphology pass rating based on the visual assessment of 6 consecutive readable PQRST complexes is at least [redacted]. The majority result from the pass/fail readings of the 3 independent, certified cardiac technicians will be used for analysis. The hypothesis for this objective is stated as follows:

[redacted]

The second hypothesis will be based on the results of the quantitative analysis of the R-wave amplitudes as measured by each of 3 independent, certified cardiac technicians on the paired ECG app and Lead 1 from the 12-Lead ECG reference strips. The majority result from the three

technicians (i.e., if at least two technicians measured the difference in amplitudes between the SUT and reference strips to be ≤2 mm then the paired strips for a given subject were deemed ≤2 mm) was used for [redacted]

For each subject, the QRS complex from the 12-lead ECG with the largest R amplitude (out of the two QRS complexes with R-wave amplitude measurements) will be used for purposes of determining the majority result.

Data from the first trial run of the randomly selected subjects while the subject is at rest and after exercise will be used to test the two waveform assessment hypotheses using a bootstrap sampling approach. If the 2.5th percentile of the bootstrap distribution for the Morphology Pass Rating Proportion [redacted] the null hypothesis H_{0_2e} will be rejected. [redacted] to the evaluation of the R-Wave Amplitude Agreement Proportion.

6.2.3. Safety Analyses

All adverse events will be recorded throughout the entire study period, whether they are considered to be related to the study procedures or not. Signs and symptoms of each AE will be described in detail: date of event, description of event, severity, relationship to study procedures, action taken and outcome. Adverse events will be collected as spontaneously reported by the subjects.

The number of any adverse events and the number and percentage of subjects reporting each type of adverse event will be presented by Preferred Term. Multiple occurrences of the same event reported by the same subject will be counted only once.

6.2.4. Additional Analyses

The following additional analyses will be performed.

- Percent correct associated with the Other abnormal rhythm truth category will be estimated as n77/(N7 - n87).
- Percent correct associated with the HR under 50 (HR<50 on simultaneous 12-lead ECG) truth category will be estimated as n11/(N1-n81).
- Percent correct associated with the HR over 150 (HR >150 on simultaneous 12-lead ECG) truth category will be estimated as n66/(N6-n86).
- Percent correct associated with the AF rhythm classification for adjudicated heart rate values between 50-120. The numerator of this percent correct calculation will be the number of test device classifications of AF and test device heart rate between 50-120 with an adjudicated AF rhythm classification and adjudicated heart rate value between 50-120. The denominator will include all classifiable test device results with an adjudicated AF rhythm classification and adjudicated heart rate between 50-120.

Two-sided 95% bootstrap confidence intervals will be constructed during the same bootstrap sampling procedure outlined for the primary and secondary endpoints for these four additional analyses. If the number of samples within any of these categories is ≤20, only summary statistics will be presented.

- The number and percentage of the ECG app Inconclusive and the ECG app Poor Recording trials within each category of ground truth will be reported as well as overall as a percentage of the total number of trials.
- A cross-classification table of the ECG app results with each of the types of Other abnormal rhythm truth categories (outlined in Section 5.2.3.1.2) will be presented.
- Descriptive summary statistics (N, mean, std. dev, min, max) of the paired heart rate differences (bpm) between the ECG app and the 12-Lead ECG will be reported by cohort and overall.

6.3. Sample Size Determination

[redacted] The sample sizes to achieve 80% power with one-sided type I error of 0.025 using exact binomial test are [redacted] subjects with no known diagnosis of AF and [redacted] subjects with a known diagnosis of AF.

Table 3 below presents the expected percent correct associated with the four secondary endpoints 2a, 2b, 2c, and 2d are summarized below along with the proposed performance goals.

[redacted]

[redacted] To account for obtaining readable/classifiable waveforms and to ensure enough data is collected from the exercise stage, 168 subjects with no known diagnosis of AF and 400 subjects with a known diagnosis of AF will be enrolled.

[redacted]

[redacted] To account for obtaining readable waveforms and to assess waveform equivalence across a range of heart rates and rhythms, approximately 100 subjects (50 SR; 50 AF) will be randomly selected according to the sampling scheme presented in Section 3.4.

6.4. Significance Level

The primary endpoint hypothesis, the four secondary endpoint hypothesis tests of percent correct, and the two secondary endpoint hypotheses of waveform assessment will use a one-sided significance level of 0.025.

6.5. Missing Data

Rigorous efforts will be made to ensure all subjects are compliant with the protocol. However, some subjects may drop out prematurely or some planned measurements may not be analyzable due to missing data or uninterpretable results from either the ECG adjudication process or the ECG app test device. The data analyses will be conducted on all analyzable data.

6.6. Subgroup Analyses

The primary endpoints will be reported by the following subgroups (data permitting). Some subgroups may be combined depending upon data availability.

- Age group (<55; ≥55 to <65; ≥65 years)
- Sex (Male; Female)
- Race (White; Black or African American; Asian, American Indian or Alaska Native; Native Hawaiian or other Pacific Islander)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino)
- Watch series/material types (Series 4, Series 5: Aluminum, ceramic, titanium, stainless steel)

6.7. Interim Analyses

There are no interim analyses planned for this study.

6.8. Analysis Sets

The following analysis sets are defined for this study.

Full Analysis Set (FAS): All subjects who sign informed consent and are enrolled into the study. This analysis set will be used to summarize subject, 12-Lead, and ECG app device accountability in addition to demographic and baseline characteristics and safety data. The data for this analysis set will be presented overall and separately for the enrollment cohorts.

Classifiable Analysis Set (CAS): All subjects with readable paired ECG app and 12-Lead ECG adjudicated results. This analysis set will be used to analyze data for the co-primary endpoints (1a, 1b), the four secondary endpoints (2a, 2b, 2c, and 2d) and the additional analyses.

Waveform Assessment Analysis Set (WAAS): Randomly selected subjects with readable paired strips from the ECG app and Lead 1 of the 12-Lead ECG. If 6 consecutive beats for analysis cannot be found in these strips, they will be excluded from analysis. This analysis set will be used for assessing the clinical waveform accuracy associated with secondary endpoints 2e and 2f.

7. SAFETY PARAMETERS AND ASSESSMENT

7.1. Adverse Events

The definition of adverse events are as follows:

Term	Definition	Reference
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the device.	ISO 14155: 2011
Serious Adverse Event (SAE)	Adverse event that a) Led to death, b) Led to serious deterioration in the health of the subject, 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: 2011

7.1.1. AE/SAE Collection

An adverse event is defined as any untoward medical occurrence (clinical symptom, sign, or significant laboratory finding, for example) in a clinical investigation subject which does not necessarily have to have a causal relationship with the study procedures.

Any abnormal laboratory findings, abnormal safety assessments, or anticipated day-to-day fluctuations which are associated with a pre-existing disease or condition, are not considered an Adverse Event unless judged by the investigator to be worsening or more severe than expected. All adverse events must be fully recorded throughout the entire study period, whether they are considered to be related to the study procedures or not. Adverse events will be collected as spontaneously reported by the subjects.

Adverse events should be followed until they are resolved or stabilized (returns to baseline for a pre-existing condition) and followed by a private MD, or the subject is lost to follow-up. In the event of a subject not returning to the clinical unit, the outcome of this event will be recorded as lost at follow up.

Possible AEs include the following:

- 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;
- Detection of atrial fibrillation or other irregular heartbeat;
- Complaint about iPhone or Apple Watch functionality;
- Study app or ECG app functionality issues that do not allege an adverse event

7.1.2. SAE Reporting

The Site Investigator should report all SAEs to the Sponsor as soon as possible but no later than 24 hours of becoming aware of the event. The Site Investigator should also report the SAEs to their IRB according to their IRB reporting requirements. On the date the Site Staff became aware that the event met the SAE definition as per provided in this protocol, the investigator will be requested to complete a separate SAE reporting form in addition to the information on the source documentation. The Investigator will conduct further investigation of these events regarding determination of event as a serious adverse event and determination of relatedness of the event to the study. The investigation of these events will be completed and reported to the Sponsor within 15 days of initial report to Sponsor.

7.1.3. Reporting of all other Study Adverse Events

Possible adverse events (non-serious) related to the study will be reported to the Sponsor within 14 business days of being reviewed by the Investigator. The Investigator will conduct further investigation of these events regarding determination of event as a serious adverse event and determination of relatedness of the event to the study. The investigation of these events will be completed and reported to the Sponsor within 30 days of initial report to the Sponsor.

Any technical issues / complaints related to the ECG app should be referred to AppleCare, 1-800-275-2273.

7.2. Safety Plan

The clinical staff is responsible for the ongoing safety and well-being of the subjects during study participation. Management of all medical complications arising during the course of the research study will be managed by the investigator as deemed appropriate. A medical monitor will be available for consultation related to subject safety and adverse events. All incidental findings identified during screening will be referred at the investigator's discretion to the appropriate additional care in accordance with current standard of care. This can include removal of the study associated devices, as well as other measures as required. Even if a study device is removed prior to the specified duration, data may be used if of suitable quality. Replacement of the study subject who has had the device removed prematurely will be as deemed appropriate, following review of the data.

7.3. Overview of study suspension and termination criteria

The research study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information regarding the safety or performance of the study becomes available in such a way that the research study is deemed unsafe or ineffective;
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety;
- Failure to meet expected enrollment goals;
- Administrative reasons.

8. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

8.1. Institutional Review Board

IRB approval for the protocol, ICF and any subject facing materials will be obtained by the Site Investigator at each Investigational sites prior to participation in the study. The IRB approval letter must be received at the Investigational site prior to starting the study, and a copy must be provided to the Sponsor. No changes will be made to the Protocol, ICF or subject facing materials without appropriate approvals, including the IRB, and Sponsor's approval.
Until study completion, the site Investigator will inform/advise his IRB of the study progress, per their IRB requirements. Further, any amendments to the protocol, as well as the associated ICF, and subject facing materials will be submitted to IRB and written approval obtained prior to implementation in the study.

The submitted documents will include but are not limited to:

a. The final protocol
b. IRB application forms
c. Informed Consent Form (ICF)

The study will not begin unless the IRB gives a favorable opinion of the study.

8.2. Informed Consent

All information about the study, including the subject information and the informed consent form (ICF), is prepared and used for the protection of the human rights of the subject according to International Council for Harmonisation (ICH) GCP guidelines and the Declaration of Helsinki.

It is the responsibility of the Investigator to obtain signed ICFs from each subject participating in this study after adequate explanation of the aims, methods, and objectives of the study and before undertaking any study-related procedures.

The ICF, prepared by the Investigator with the assistance of the Sponsor, must be approved along with the study protocol by the IRB and be acceptable to the Sponsor.

The subject must be provided with the subject information and ICF consistent with the study protocol version used and approved by the relevant IRB. The ICF must be in a language fully comprehensible to the prospective subject. Subjects must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their participation in the study with the Investigator concerned. The subject and the person explaining about the study and with whom they discuss the informed consent will sign and date the ICF. A copy of the signed and dated ICF will be retained by the subject and the original will be filed in the Investigator file unless otherwise agreed. New information will be provided in written form to the subject.

8.3. Record Keeping

This study will be conducted in accordance with GCP guidelines. Trial documents should be retained until at least 2 years after the last approval of marketing application in an ICH region and until there are no pending or contemplated-marketing applications in an ICH region. If there are no local laws, sites should retain filed for 5 years after completion of the study. Records include informed consent, protocols, and electronic case report forms (eCRFs).

8.4. Confidentiality and Privacy

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor and its agents. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor. Compliant with Health Insurance Portability and Accountability Act of 1996 (HIPAA) guidelines, only certified copies of coded data will be sent from the study site to the cardiology reviewers. Under no circumstances, except when legally compelled, will any healthcare provider of any enrolled subject be allowed to receive specific outcome data for that subject.

8.5. Protocol Adherence

The protocol must be read thoroughly in its entirety and instructions followed exactly. Any deviations should be agreed on by Sponsor and the Investigator and reported to IRB as per their reporting guidelines, with the appropriate written and approved protocol amendments made to reflect the agreed upon changes. Where the deviation occurs for the well-being of the subject, the Sponsor must be informed of the action taken. Actions taken for the well-being of a subject may occur before the sponsor is notified.

8.6. Collection and Management Responsibilities

Data will be collected using eCRFs in a validated system. The Sponsor or designee will supply the eCRFs. All eCRFs should be completed by designated, trained personnel, as appropriate. All changes or corrections to the eCRF will be documented via a data correction form (query) with an audit trail and adequate explanation for the revision is required. eCRFs will be signed and dated by the Principal Investigator or designee.

The investigator(s) will permit trial-related monitoring, audits, IRB review and regulatory inspections(s), providing access to data documents. Members of the investigational site team and their designated authorization(s) will be identified in a log.

Access to data collection devices will be controlled and the devices will be used only in the clinical investigation and according to the clinical investigation plan. The investigator or authorized designee will keep records documenting the receipt, use and return of the study-related data collection devices.

8.7. Study Monitoring

On behalf of the Sponsor, a CRO monitor will contact and visit the investigator(s) at the study site(s) before the entry of the first subject and at predetermined appropriate intervals during the

study until after the last subject has completed. The monitor will also perform a study closure visit.

Prior to starting the study, the Investigator understands and accepts the obligation to conduct the study according to the Protocol and applicable regulations, and has signed the Investigator Agreement. In accordance with ICH GCP guidelines, the investigators must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol, including the safety and well-being of subjects, and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The investigator will make all source data (i.e., the various study records, ICF, eCRFs, other subject records, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the subjects with the entries on the eCRF (i.e., source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs.

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved in a reasonable period of time. Contact information for the study monitor is located in the investigator file. Representatives from the Sponsor may also contact and visit the investigators and monitor data during the study.

8.8. Data Quality Assurance and Quality Control

The Sponsor or designee will perform internal quality management of study conduct, and data collection, documentation and completion. Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to study staff for clarification/resolution.

8.9. Use of Information

All information concerning the study devices, equipment and the Sponsor is considered confidential information. The information developed during the conduct of this clinical trial is also considered confidential and will be used by the Sponsor in connection with the development of the study device as described in this protocol. This information may be disclosed as deemed necessary by the Sponsor to allow the use of information derived from this clinical study and to ensure complete and thorough analysis. The investigator is obligated to provide the Sponsor with complete study results and all data developed in this study.

[redacted]

This confidential information shall remain the sole property of the Sponsor and shall not be disclosed to others without the written consent of the Sponsor and shall not be used except in the performance of this study.

8.10. Study Record Retention

All data collected or derived from this research study will remain the property of the Sponsor.

Any and all correspondence relating to this research study, for example with the Sponsor or the IRB, should be kept in the appropriate file folders at the CRO. Records of research study subjects' source documents which pertain to the research study must be kept on file at the CRO.

Records must be maintained according to the guidelines of the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP).

8.11. Study Termination and Site Closure

The Sponsor and the investigators reserve the right to terminate the study or participation in the study, respectively, at any time. Both parties will arrange discontinuation procedures. In terminating the study, the Sponsor and the investigators will assure that adequate consideration is given to the protection of the subjects' interests.

The Sponsor reserves the right to discontinue the study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be given.

The entire study will be stopped if:

- Evidence has emerged that, in the opinion of the Sponsor or the investigator(s), makes the continuation of the study unnecessary or unethical;
- The stated objectives of the study are achieved;
- The development of the study device is discontinued.

Regardless of the reason for termination, all data available for subjects at the time of discontinuation of follow up must be recorded on the eCRF. All reasons for discontinuation of treatment must be documented.

8.12. Completion of the Study

The investigator(s) agree to provide financial disclosure forms and to complete this study in satisfactory compliance with the protocol and all applicable regulatory requirements within the timeframe allotted in the financial contract. Delays in the completion and/or reporting of the study beyond this time must be mutually agreed upon in writing by both the investigator and the Sponsor.

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1. TABLE OF EVENTS

	Screening	Study Day[3]

Procedure	Before Enrollment	In-Lab
Informed Consent	X	
I/E Criteria Assessment	X	
Medical History including allergies	X	
Demographic information	X	
12-lead ECG	X	X[2]
Vital Signs	X	
Urine Pregnancy Test[1]	X	
Wrist/Hand Assessment (Dominant hand, skinfold thickness, wrist circumference, wrist hairiness, tattoos)	X	
Physical examination (will include at a minimum general appearance, lungs, chest, heart, head and neck, abdomen, musculoskeletal/extremities, lymph nodes, skin and neurological assessment)	X	
Social History (smoking status, alcohol use, recreational drug use, caffeine intake)	X	
Body Measurements and Assessments (anthropometrics) (height, weight, BMI)	X	
Concomitant Medications	X	X[2]
Dispense Study Equipment, test set-up, record device ID assigned to subject		X
Record watch series, size, watch material (aluminum, steel, etc.)		X
Record subject choice of wrist for device. Default is left wrist		X
Take baseline resting heart rate		X
Practice taking ECG reading		X
Collect ECG reading with both device and 12-lead ECG - 3 trials		X
Practice exercise trial to determine resistance/speed		X
Collect ECG reading after each exercise trial with both device and 12-lead ECG - 3 trials		X

Detach 12-lead ECG		**X**
Remove wrist device		**X**
Transfer data from wrist device to paired smartphones		**X**
Record Adverse and/or Serious Adverse Events		**X**
Disposition Status Assessment		**X**

[1]For women of child-bearing potential only. A woman will be considered not of child-bearing potential if they are surgically sterile and have provided documentation, or they are ≥55 and have not had a cycle for ≥2 years.

[2]Only needed if study day is different from screening day

[3] Study Day can be on the same day or different day than the Screening Day.