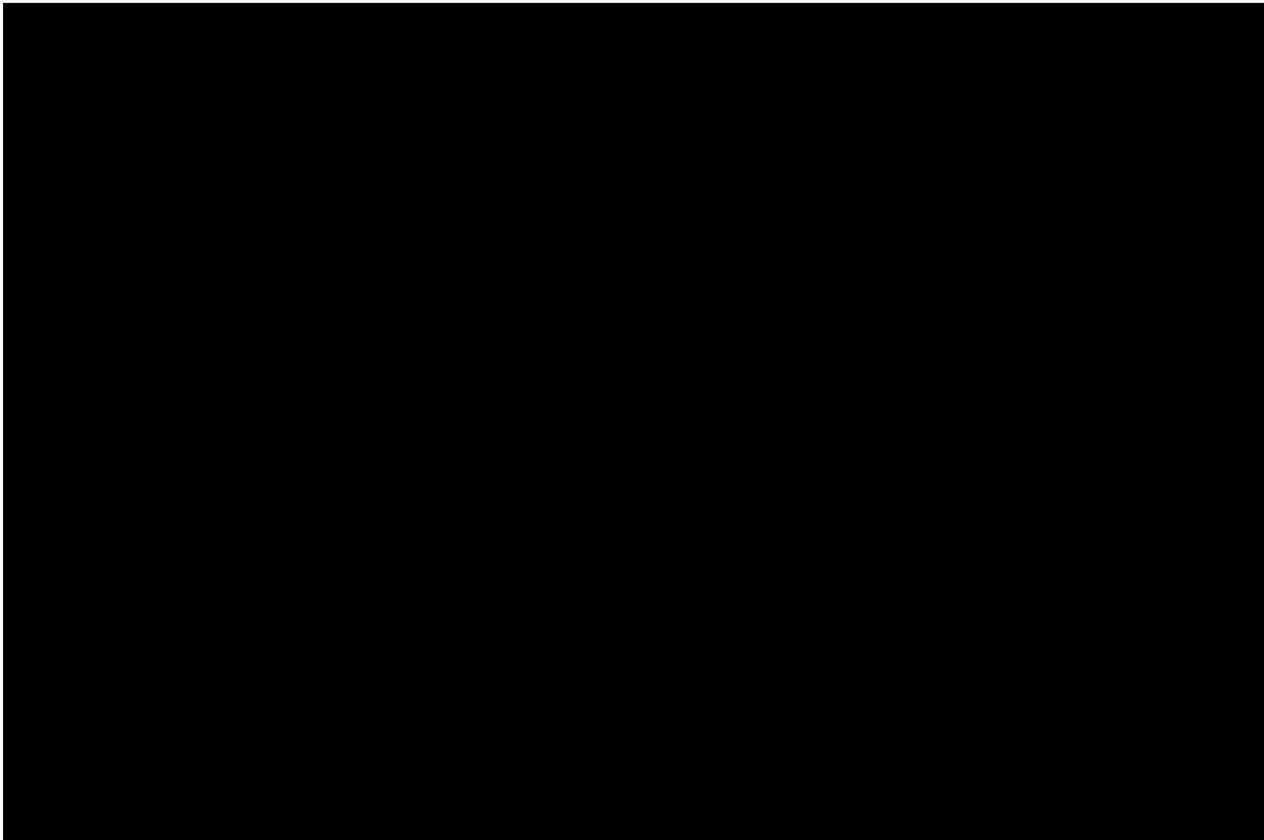Electrocardiogram Clinical Validation Study

NCT03492554

15Jun2018

# Electrocardiogram Clinical Validation Study

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|---|---|
| **Sponsor:** | **New Atlantis Research** |
| **Protocol Number** | **099-11774** |
| **Version and date:** | █ **15 June 2018** |
| **Compliance Statement:** | This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the U.S. Food and Drug Administration (21 CFR Parts 50, 54, 56, and 812), and ICH GCP Guidelines. |
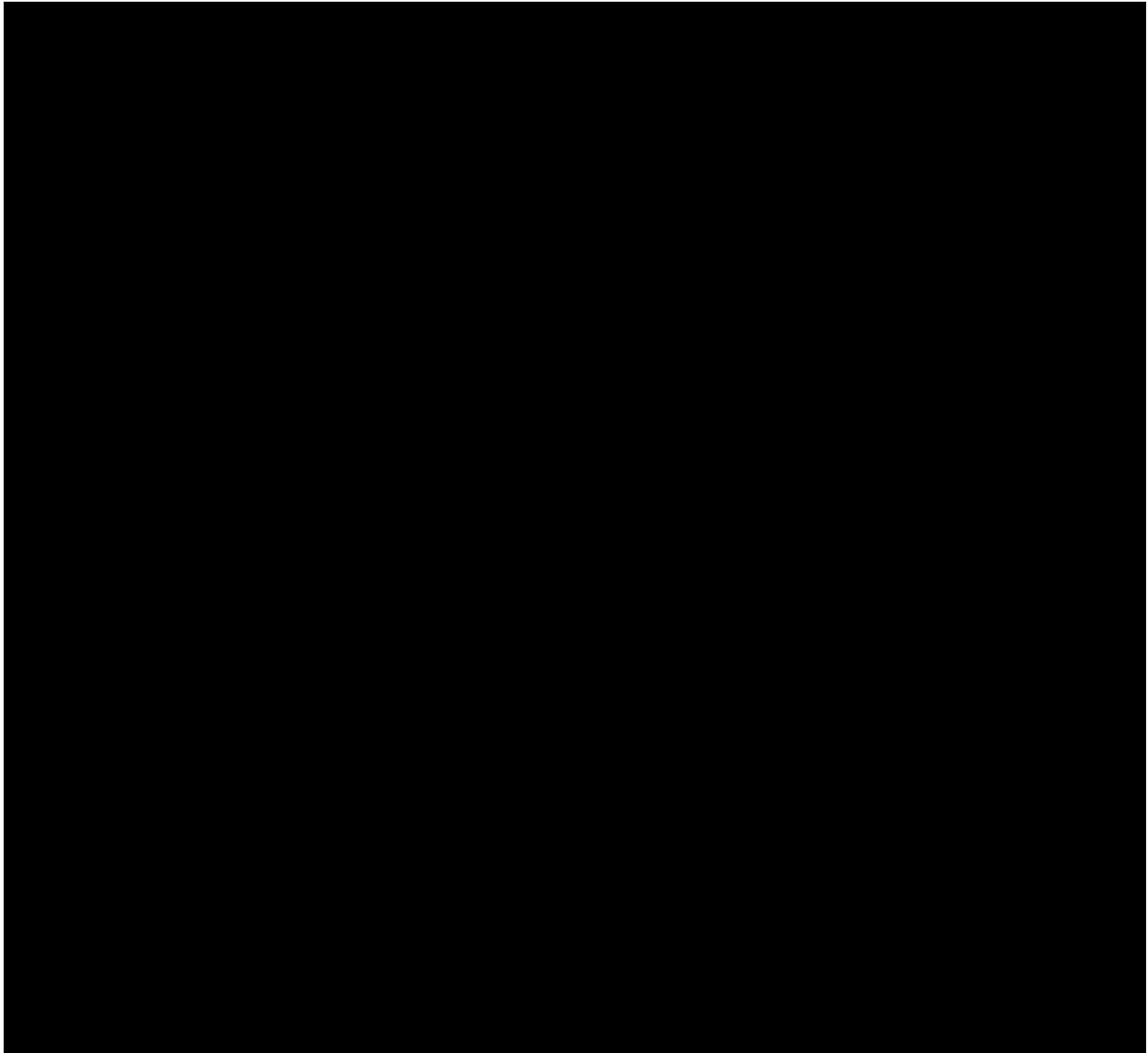
# INVESTIGATOR APPROVAL PROTOCOL SIGNATURE PAGE

**Protocol:**   **099-11774**
**Title:**    Electrocardiogram Clinical Validation Study

**Amendment:**   N/A

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 Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and U.S. Code of Federal Regulations applicable to clinical studies (21 CFR Parts 50 (protection of human subjects), 54 (financial disclosure by clinical investigators), 56 (informed consent and 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 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:


_____        _____
Investigator's Signature                                                    Date


_____
Name/Title

# SYNOPSIS
## Electrocardiogram Clinical Validation Study

**Overview**

The purpose of this study is two-fold:

1) To validate a rhythm classification algorithm and its ability to detect and classify heart rhythms into one of two categories (sinus rhythm [SR] and atrial fibrillation [AF]) using a single Lead I ECG strip.

2) To validate the software's ability to generate a Lead 1 electrocardiogram (ECG) that is clinically equivalent to a standard 12-lead ECG.

**Study Objectives**

1) The primary objective is to demonstrate that the software under testing (SUT) has acceptable sensitivity and specificity;

2) Secondary objectives are

   a. To demonstrate that the SUT produces a waveform that provides clinically equivalent information to the gold standard.

   b. To understand ease of use between three different data collection devices.

**Study Endpoints**

1) Primary endpoints: Sensitivity, specificity

2) Secondary endpoints: clinically equivalent waveform, ease of use

**Study Hypotheses**

1) The primary hypothesis is that the SUT will have >90% sensitivity and >92% specificity in detecting AF on "readable and classifiable" strips generated by a single Lead I ECG.

2) The secondary hypothesis is that the SUT produces a waveform that provides clinically equivalent information to the gold standard.

**Subject Population**

Study cohorts and target population

- Study subjects

  o A minimum of 260 subjects (up to a maximum of 400 subjects) with AF

    ▪ A population of subjects with a known diagnosis of AF (permanent or persistent AF as the likelihood of being in AF during data collection is higher)

  o Approximately 300 subjects with SR

    ▪ A population of subjects with no known diagnosis of AF

- There is no age distribution requirement for the AF population. For subjects with SR, there will be at least 25 subjects in each of the 22-30, 31-50, 51-64 categories and at least 150 subjects in the 65+ category.

- Men and women should be equally represented between the two study cohorts with a goal of having women represent >30% of subjects.

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

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. This location is determined by asking the volunteer to put on a normal wrist-watch and marking the skin with a pen/marker to outline the edges of the band.)

6. For subjects enrolled into the AF population, subjects must have a known diagnosis of AF and be in AF at the time of screening. Subjects may have any type of AF including paroxysmal, persistent, and permanent AF although persistent and permanent AF are preferred as they are more likely to be in AF at the time of screening.

Exclusion criteria

Subjects who meet any of the following criteria may not be enrolled:

1. Physical disability that precludes safe and adequate testing

2. Mental impairment resulting in limited ability to cooperate

3. Subjects with a pacemaker or implantable cardioverter-defibrillator (ICD)

4. Acute myocardial infarction (MI) within 90 days of screening or other cardiovascular disease that, in the opinion of the Investigator, increases the risk to the subject or renders data uninterpretable (e.g., recent or ongoing unstable angina, significant valvular heart disease or heart failure, myocarditis or pericarditis)

5. Acute pulmonary embolism, pulmonary infarction, or deep vein thrombosis within 90 days of screening

6. Stroke or transient ischemic attack within 90 days of screening

7. Subjects taking rhythm control drugs (e.g., disopyramide, quinidine, flecainide, propafenone, amiodarone, dofetilide, dronedarone, sotalol, procainamide, ibutilide, moricizine, procainamide). An exception will be made for subjects who are undergoing scheduled cardioversion for known AF within 30 days after study participation. These study participants will be allowed to participate in the study even when on rhythm control drugs.

      a.  Rate control and anti-coagulants, anti-platelet medications are permitted (e.g., metoprolol, atenolol, diltiazem, coumadin, clopidogrel, aspirin)

8.  Symptomatic (or active) allergic skin reactions such as eczema, rosacea, impetigo, dermatomyositis or allergic contact dermatitis on both wrists or over electrode attachment sites

9.  Known sensitivity to medical adhesives, isopropyl alcohol, watch bands, or electrocardiogram (ECG) electrodes including known allergy or sensitivity to fluoroelastomer bands primarily used in wrist worn fitness devices

10. A history of abnormal life-threatening rhythms as determined by the investigator (e.g., ventricular tachycardia, ventricular fibrillation, 3<sup>rd</sup>-degree heart block, resting heart rate < 50 beats per minute (bpm), resting heart rate >110 bpm)

11. Significant tremor that prevents subject from being able to hold still

12. Pregnant women: Women who are pregnant at the time of study participation.

13. ████████████████████████████████████████

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15. For subjects enrolled into the sinus rhythm population, they must not have any diagnosis of AF. For example, subjects cannot be enrolled into the sinus rhythm population if they have a diagnosis of paroxysmal AF but during screening are in sinus rhythm.

**Study Details**

<u>Screening for Participation</u>

Subjects should be screened based on the above inclusion and exclusion criteria.

Informed consent will be obtained before any study protocol-directed procedures are performed. After the signing of informed consent, the subject's eligibility based on the inclusion/exclusion criteria will be evaluated.

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

- Age
- Gender
- Race and ethnicity
- Occupation
- Diagnosed medical conditions

- Medications
- Allergies
- Smoking history
- Alcohol Use (self reported)
- Recreational Drug Use (self reported)
- Brief physical examination
- Height and weight
- Body mass index (BMI)
- Vital signs will be collected after sitting for at least 5 minutes (blood pressure with systolic recorded within the range of 80-180 mm Hg and diastolic recorded in the range of 40-120 mmHg, heart rate recorded within the range from 50-110 beats per minute, temperature recorded within range of 35.5-37.5 degrees)
- Urine pregnancy testing for women of childbearing potential
- Caffeine intake
- Exercise habits
- Dominant hand
- Wrist circumference (for wrist that device will be worn on)
- Skin fold thickness (for wrist that device will be worn on)
- Wrist hairiness (for wrist that device will be worn on)
- 12-lead ECG will be collected supine after lying for at least 5 minutes

All volunteers will undergo a 12-lead ECG. The 12-lead ECG will be reviewed live by study personnel. AF subjects must be in AF at the time of the 12-lead ECG in order to be assigned to the AF population. If subjects are not in AF at the time of the 12-lead screening ECG, they may be re-screened for participation at a later date.

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

Day of participation

- No special preparation for this visit is required.

- All subjects may take their normal medications the day of the study.

- All subjects may eat normally.

- All subjects will be asked to remove jewelry and any underwire bras during active data collection.

- It is recommended that participants wear t-shirt and shorts during data collection.

Study Procedures

Data collection device set up: The data collection device consists of two dry electrodes built into a smartwatch. It allows for the collection of raw single-lead ECG data that are then processed by

the software under testing (SUT) to produce a Lead-1 ECG as well as a rhythm classification of the waveform.

1. Hand subject a watch and ask subject to place it on his/her preferred wrist. Observe how the subject places the watch on their wrist.

2. Assign a device to each subject and document the device number.

3. Instruct the subject to choose his/her preferred wrist to wear the data collection device (DCD). The DCD 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 device must be worn on the non-affected wrist. Record the subject's choice of 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.

4. Study staff will place the DCD on the study participant's wrist (as indicated in 3.) The device should be fitted tightly enough that it does not move when the hand/wrist is shaken.

5. Check band tightness for a snug fit and adjust as needed.

6. Instruct the subject to read the provided instructions on how to record a single-lead ECG. The written instructions are:

   a) "It takes 30 seconds to record a measurement. It's important to keep your arms still. Try resting them on a table or your leg. To begin recording rest your finger on the knob."

   b) Practice data will be recorded.

7. After the first practice run, site study staff will guide subject to appropriate study posture and grip (if not achieved independently during the first test run).

8. Allow subject up to three additional practice runs if more practice runs are needed to ensure study posture and grip instruction understanding (fewer than 3 additional practice runs are acceptable if study posture and grip are correct and subject is comfortable with the positioning),

9. Record the number of practice runs completed by the subject. First practice run data and number of practice runs completed by the subject will be used to determine ease of use.

*Data collection:*

10. Instruct subject to remain seated for a 5-minute resting period prior to collecting three 12-lead ECGs and set the reference system to 40 Hz filter. Use standard placement of all 12-lead electrodes (with limb lead for Lead 1).

11. Collect 3 separate complete 12-lead ECGs (review to ensure there is no artifact). Each recording will be approximately 30 seconds in duration with a 1-minute rest period between each recording (i.e., 1 minute between the end of the previous recording and the start of the next recording). Simultaneously, instruct the subject to record 3 separate complete single-lead ECGs using the DCD. A total of three complete single-lead ECGs

will be collected for each subject. Each recording will be approximately 30 seconds in duration with a 1-minute rest period between each recording (i.e., 1 minute between the end of the previous recording and the start of the next recording). Each recording will correspond to the time of collection of each 12-lead ECG recording.

   a) Monitor the 12-lead waveform to ensure a good quality recording is obtained.

   b) Monitor the waveform from the Lead 1 ECG from the DCD, between ECG recordings, provide feedback to the subject on how to improve the reading.

12. After data collection, instruct study subjects to rate the ease of use of the DCD on a scale of 1-5 (1 being Unable to Use, 2 being Below Average Ease of Use, 3 being Average Ease of Use, 4 being Above Average Ease of Use, 5 being Easiest to Use). Record the rating in the eCRF. Remove DCD from subject.

13. Instruct study subjects to apply and simulate a recording with each of the other devices ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ to rate the comfort and ease of use of each of these devices on a scale of 1-5 (scale is listed above in #10). Record the ratings.

*Data Processing:*

14. The Sponsor will receive data files from:

   a) The reference device 12-lead ECG files

   b) Raw data DCD files

15. The Sponsor will check data for Protocol and MOP adherence.

16. For Part A (described below), the Sponsor will sync Lead 1 of the 12-lead (reference strip) to the corresponding SUT's strip to ensure that the same beats from each subject are presented.

17. The Sponsor will provide a PDF of the full 30-second strip of both the reference strips and the SUT's strips on the standard clinical ECG scale to Cardiac Core Lab (for each of Part A, Part B-1, and Part B-2).

18. Cardiac Core Lab will print the strips for analysis and distribute to appropriate experts for review.

*Data Review by Cardiac Core Lab: (refer to Operations Plan/Imaging Charter)*

19. **Part A** (To address Objective 2a): Analysis of paired sets of strips.

   a) The Sponsor will prepare one paired set of strips from approximately 140 randomly selected subjects (70 AF, 70 SR) (approximate strips = 280)

      i.   One set includes a Lead 1 strip from the 12-lead and a paired strip from the SUT.

      ii.  The first reading from data collection will be used for all subjects.

   b) Cardiac Core Lab review:

      i.    Three independent cardiac technicians will review each paired set of strips. The strips will be rendered semi-transparent through the use of back lighting and overlaid to visually assess for morphological similarity.

      ii.    One reviewer will identify the first six consecutive distinct readable PQRST complexes without artifact that match between the strips 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 SUT 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 strip 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.

      iii.    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.

      iv.    Measure R amplitude from the isoelectric baseline to the nearest millimeter for the first two QRS complexes in both the reference strip and SUT strip (reviewers will be blinded to the identity of the reference strip and SUT strip). Record these lengths.

20. **Part B-1** (To address Objective 1): Analysis of reference strips.

    a)    The first reading from 12-lead ECG data collection will be used for all subjects (total strips = ~560). In the event that the planned sample size for analysis is not obtained due to a higher than expected amount of data loss, the 2nd and 3rd reading from data collection may be used as described in the statistical analysis plan (SAP).

    b)    A pool of 3 to 9 blinded independent U.S. board-certified cardiologists will review each complete 12-lead ECG (reference strip) and provide a diagnosis of the rhythm. (i.e. Each reference strip will be reviewed independently 3x)

    c)    The diagnosis of the rhythm will fall into one of four categories

      i.    Sinus rhythm (SR)

      ii.    AF

      iii.    Other specific diagnoses should be called out (examples include normal sinus with premature ventricular contraction [PVC] (if ≥4 beats in the strip), normal sinus with PACS, 2nd degree block, AF with a rate >150 bpm, supraventricular tachycardia [SVT], etc.)

      iv.    Unreadable = a diagnosis cannot be made as the strip is not adequate for reading.

21. **Part B-2:** Analysis of SUT's strips.

    a)    The first reading from the SUT's Lead I ECG will be used for all subjects (total strips = ~560).

    b) A pool of 2 to 5 blinded independent cardiologists will review each of the SUT's strips (single-lead ECG strip generated by the Sponsor's system) and provide a diagnosis. Diagnoses are listed above under #20c (total strips = ~560)

22. **Part C:** Algorithm classification

    a) The Sponsor will generate a rhythm classification (through use of the algorithm) for the strips that match those strips analyzed in Part B-1 from the SUT for all subjects. (hereon referred to as algorithm classification) (total strips = ~560)

    b) The rhythm classification generated by the algorithm will fall into one of four categories:

        v.    Sinus rhythm (SR)

        vi.    AF

        vii.    Unclassifiable = Other specific diagnoses which are not AF or SR (examples include normal sinus with premature ventricular contraction [PVC] (if ≥4 beats in the strip), normal sinus with PACS, 2nd degree block, AF with a rate >150 bpm, supraventricular tachycardia [SVT], etc.)

        viii.    Unreadable = a classification cannot be made as the strip is not adequate for reading.

    c) The Cardiac Core Lab will not review the rhythm classifications.

**Required equipment**

Sponsor-provided

    Data collection device (DCD) for single-lead ECG collection

    Hardware to view single-lead ECG waveforms during data collection

    Assortment of other devices for simulation

        a) Commercially available wrist-worn device ■■■■■■

        b) Commercially available handheld device ■■■■■■■■■ and companion device (tablet/phone/iPod)

Contract Research Organization (CRO)-provided

- 12-lead ECG monitor: GE Healthcare CardioSoft system. CardioSoft is an FDA-cleared ECG device (K031561).
- Secure Network Attached Storage (NAS)

Investigational Study Site - provided

- Space to screen subjects

- Space to conduct testing and regular exam room/office equipment

- Equipment to record vital signs

- Appropriate safe and storage area for devices.


**Statistical Analyses**

Details of planned statistical analyses are included in the body of the protocol (Section 5.3).

# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

**Abbreviations and Definitions of Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AF | atrial fibrillation |
| CRO | contract research organization |
| DCD | Data Collection Device |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| GCP | Good Clinical Practice |
| HCP | healthcare provider |
| HIPAA | Health Insurance Portability and Accountability Act of 1996 |
| ICD | implantable cardioverter-defibrillator |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IRB | Institutional Review Board |
| MI | myocardial infarction |
| Ms | millisecond(s) |
| NAS | Network Attached Storage |
| NSR | normal sinus rhythm |
| PAC | premature atrial contraction |
| PQRST | A full beat on the ECG including the p wave, QRS complex, and T wave. |
| PVC | premature ventricular contraction |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| QC | quality control |
| R amplitude | The height of the R wave measured from the baseline to the peak of the R wave. |
| SUT | Software under development |
| SVT | supraventricular tachycardia |
| 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, many affected with AF are unaware they have this dysrhythmia due to a number of factors including lack of symptoms, or experience only mild symptoms that they do not attribute to a disease[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 the SUT can facilitate identification of AF.

## 1.2.      Device Description

The data collection device includes electrodes that can be used to obtain heart rate and lead I ECG information. A user can use the device to take an ECG measurement by wearing it on their wrist while placing the finger of the opposing hand on an accessible electrode of the device.

The software under testing analyzes the acquired single channel ECG signals and detects the presence of AF and SR for each ECG recording.

## 1.3.      Study Rationale

AF increases the risk of heart failure by 11 per 1000, kidney problems by 6 per 1000, death by 4 per 1000, stroke by 3 per 1000, and coronary heart disease by 1 per 1000. However, if detected, treatment of AF with oral anticoagulation is effective in reducing stroke risk by approximately two-thirds and death by almost one-third. Studies have shown that systematic screening, where an ECG is taken for all patients, yields a higher rate of AF detection when compared to opportunistic screening, where an ECG is taken only if the standard pulse taking yields an irregular pulse. Therefore, widespread screening for AF by an easy-to-use device can potentially result in improved detection, leading to more effective treatment and improving

health outcomes. The purpose of this study is to aid in the development of a system that reads ECG signals and is capable of detecting AF.

## 1.4.        Risk/Benefit Assessment

No significant risks or permanent side effects are anticipated. However, participants 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 as well as mild skin irritation from the wristband of the data collection device. The risk will be minimized by using medical-grade disposable electrodes and both electrodes and wrist bands will be attached to the skin only for the limited study duration. Temporary skin irritation may still occur locally at the sites where the electrodes are placed or the band is worn, and will not be recorded as an Adverse Event.

## 2.         STUDY OBJECTIVES, ENDPOINTS, AND HYPOTHESES

### 2.1.         Study Objectives

The objectives of this study are:

1) The primary objective is to demonstrate that the software under testing (SUT) has acceptable sensitivity and specificity.

2) Secondary objectives are

   a. To demonstrate that the SUT produces a waveform that provides clinically equivalent information to the gold standard.

   b. To understand the ease of use between three different data collection devices.

### 2.2.         Study Endpoints

The endpoints of this study are:

1) Primary endpoints: Sensitivity, specificity

2) Secondary endpoints: clinically equivalent waveform, ease of use

### 2.3.         Study Hypotheses

The hypotheses of this study are:

1) The primary hypothesis is that the SUT will have >90% sensitivity and >92% specificity in detecting AF on "readable and classifiable" strips generated by a single Lead I ECG.

2) The secondary hypothesis is that the SUT produces a waveform that provides clinically equivalent information to the gold standard.

## 3.      STUDY DESIGN

## 3.1.      Overview

This is a non-invasive, 2-part, multi-center study. The purpose of this study is two-fold:

1) To validate a rhythm classification algorithm and its ability to detect and classify heart rhythms into one of two categories (SR or AF) using a single Lead I ECG strip.

2) To demonstrate that the SUT produces a waveform that provides clinically equivalent information to the gold standard.

Eligible subjects will be enrolled and scheduled to attend a single day of participation at the clinic (Section 5.2). Subjects will wear the data collection device (DCD) on their wrist and record 3 single-lead ECGs using the DCD while the study staff simultaneously records three 12-lead ECGs.

In Part A of the study, 3 blinded, independent cardiac technicians will review paired sets of SUT strips and Reference strips from a subset of approximately140 randomly selected subjects (70 SR; 70 AF) in order to address objective 2a (Section 2). The strips will be rendered semi-transparent through the use of back lighting and overlaid to visually assess for morphological similarity. The cardiac technicians will assign a pass/fail to the strips by visually assessing 6 consecutive readable PQRST complexes.

In Part B-1 of the study, each 12-lead ECG reference strip will be reviewed 3x by blinded, independent U.S. board-certified cardiologists to provide a diagnosis of the rhythm according to the categories presented in Section 5.2.1.4, Item 20c.

In Part B-2 of the study, at least 2, but up to 5 blinded, independent cardiologists will review each of the SUT's strips (single-lead ECG strip generated by the Sponsor's system) and provide a diagnosis of the rhythm according to the categories presented in Section 5.2.1.4, Item 20c.

In Part C of the study, the Sponsor will generate a rhythm classification through the use of an algorithm (hereon referred to as algorithm diagnosis).

## 3.2.      Required Equipment

All data collection devices and the SUT will be identical in design and function and will be returned to the Sponsor at the end of the evaluation.

### 3.2.1.      Sponsor-provided

The Sponsor will provide the study sites with:

- Data collection device (DCD) for single-lead ECG collection

- Hardware to view single-lead ECG waveforms during data collection

- Assortment of other devices for simulation

    a) Commercially available wrist-worn device ███████████

    b) Commercially available handheld device █████████████   and

companion device (tablet/phone/iPod)

### 3.2.2. Contract Research Organization (CRO)-provided

The CRO will provide:

- 12-lead ECG monitor: GE Healthcare CardioSoft System. CardioSoft is a FDA cleared ECG device (K031561).

- Secure Network Attached Storage (NAS)

Investigational Study Site - provided

- Space to screen subjects

- Space to conduct testing and regular exam room/office equipment

- Equipment to record vital signs

- Appropriate safe and storage area for devices

## 3.3. Qualification Criteria for ECG Operators and Independent Cardiologists

Only individuals trained by the Sponsor or its designee(s) will be qualified to assume the role of an ECG operator or independent cardiology reviewer. ECG operators may include appropriately trained technicians, students, nurses, and/or physicians. Cardiac technicians must be Certified Cardiographic Technicians. Cardiology reviewers may include physicians experienced in reading ECG leads in order to make diagnostic determinations of adult patients. Cardiology reviewers must be a licensed medical doctor specialized in cardiology.

Information regarding the specific training, years of experience, and specialty of each reviewer will be collected.

## 3.4. Randomization and Blinding

This study is not randomized.

Cardiac technicians will be blinded in Part A and will not know which strip is the reference vs SUT strip.

U.S. board-certified cardiologists in Part B-1 and board-certified in Part B-2 will be blinded to the subject's past medical history and algorithm classification.

## 3.5. Duration of Subject Participation

Subjects will participate in a screening visit and, if eligible, participate in the study at the same visit. Participants with AF who are not in AF at the time of screening will be eligible for re-screening and participation at a later date.

## 4.        STUDY POPULATION

## 4.1.        Number of Subjects and Subject Recruitment

Subject recruitment can be accomplished in any appropriate fashion, within the guidelines of the central Institutional Review Board (IRB).

## 4.2.        Study Cohorts and Target Population

The study will include 2 cohorts:

- A minimum of 260 subjects (up to a maximum of 400 subjects) with AF

    o    A population of subjects with a known diagnosis of AF (permanent or persistent AF as the likelihood of being in AF during data collection is higher)

- Approximately 300 subjects with SR

    o    A population of subjects with no known diagnosis of AF

- There is no age distribution requirement for the AF population. For subjects with SR, there will be at least 25 subjects in each of the 22-30, 31-50, 51-64 categories and at least 150 subjects in the 65+ category.

- Men and women should be equally represented between the two study cohorts with a goal of having women represent >30% of subjects.

## 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

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. This location is determined by asking the volunteer to put on a normal wrist-watch and marking the skin with a pen/marker to outline the edges of the band.)

6. For subjects enrolled into the AF population, subjects must have a known diagnosis of AF and be in AF at the time of screening. Subjects may have any type of AF including paroxysmal, persistent, and permanent AF although persistent and permanent AF are preferred as they are more likely to be in AF at the time of screening.

## 4.4.        Exclusion Criteria

Subjects who meet any of the following criteria may not be enrolled:

1. Physical disability that precludes safe and adequate testing

2. Mental impairment resulting in limited ability to cooperate

3. Subjects with a pacemaker or implantable cardioverter-defibrillator (ICD)

4. Acute myocardial infarction (MI) within 90 days of screening or other cardiovascular disease that, in the opinion of the Investigator, increases the risk to the subject or renders data uninterpretable (e.g., recent or ongoing unstable angina, significant valvular heart disease or heart failure, myocarditis or pericarditis)

5. Acute pulmonary embolism, pulmonary infarction, or deep vein thrombosis within 90 days of screening

6. Stroke or transient ischemic attack within 90 days of screening

7. Subjects taking rhythm control drugs (e.g., disopyramide, quinidine, flecainide, propafenone, amiodarone, dofetilide, dronedarone, sotalol, procainamide, ibutilide, moricizine, procainamide). An exception will be made for subjects who are undergoing scheduled cardioversion for known AF within 30 days after study participation. These study participants will be allowed to participate in the study even when on rhythm control drugs.

    a. Rate control and anticoagulants, anti-platelet medications are permitted (e.g., metoprolol, atenolol, diltiazem, coumadin, clopidogrel, aspirin)

8. Symptomatic (or active) allergic skin reactions such as eczema, rosacea, impetigo, dermatomyositis or allergic contact dermatitis on both wrists or over electrode attachment sites including known allergy or sensitivity to fluoroelastomer bands primarily used in wrist worn fitness devices

9. Known sensitivity to medical adhesives, isopropyl alcohol, watch bands, or electrocardiogram (ECG) electrodes

10. A history of abnormal life-threatening rhythms a determined by the investigator (e.g., ventricular tachycardia, ventricular fibrillation, $3^{rd}$-degree heart block, resting heart rate < 50 bpm, resting heart rate >110 bpm)

11. Significant tremor that prevents subject from being able to hold still

12. Pregnant women: Women who are pregnant at the time of study participation.

13. ███████████████████████████████████████

14. ███████████████████████████████████████

15. For subjects enrolled into the sinus rhythm population, they must not have any diagnosis of AF. For example, subjects cannot be enrolled into the sinus rhythm population if they have a diagnosis of paroxysmal AF but during screening are in sinus rhythm.

## 4.5. Subject Withdrawal and Replacement

A consented, enrolled subject may withdraw from the study for any reason. Subjects who withdraw prior to participation or who fail to complete study participation will be replaced.

## 4.6. Subject Follow up

After completion of study participation, the subject is discharged from the study with no protocol-specified follow up.

## 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
- Occupation
- Diagnosed medical conditions
- Medications
- Allergies
- Smoking history
- Alcohol Use (self reported)
- Recreational Drug Use (self reported)
- Brief physical exam
- Height and weight
- Body mass index (BMI)
- Vital signs will be collected after sitting for at least 5 minutes (blood pressure with systolic recorded within the range of 80-180 mm Hg and diastolic recorded in the range of 40-120 mmHg, heart rate recorded within the range from 50-110 beats per minute, temperature recorded within range of 35.5-37.5 degrees)
- Urine Pregnancy testing for women of childbearing potential
- Caffeine intake
- Exercise habits
- Dominant hand
- Wrist circumference (for wrist that device will be worn on)
- Skin fold thickness (for wrist that device will be worn on)
- Wrist hairiness (for wrist that device will be worn on)
- 12-lead ECG will be collected supine after lying for at least 5 minutes

All volunteers will undergo a 12-lead ECG. The 12-lead ECG will be reviewed live by study personnel. AF subjects must be in AF at the time of the 12-lead ECG in order to be assigned to the AF population. If subjects are not in AF at the time of the 12-lead screening ECG, they may be re-screened for participation at a later date.

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.     Day of Participation

Subjects will report to the clinic for evaluation at their scheduled date and time. No special preparation for this visit is required. All subjects may take their normal medications on the day of the study and may eat normally the day of participation. Participants will be asked to remove jewelry and any underwire bras during active data collection. It is recommended that participants wear t-shirt and shorts during data collection.

### 5.2.1.     Study Procedures

#### 5.2.1.1.     Data Collection Device Set up

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

1. Hand subject a watch (regular wristwatch) and ask subject to place it on his/her preferred wrist. Observe how the subject places the watch on their wrist.

2. Assign a device to each subject and document the device number.

3. Instruct the subject to choose his/her preferred wrist to wear the data collection device (DCD). The DCD 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 device must be worn on the non-affected wrist. Record the subject's choice of 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.

4. Study staff will place the DCD on the study participant's wrist (as indicated in 3.). The device should be fitted tightly enough that it does not move when the hand/wrist is shaken.

5. Check band tightness for a snug fit and adjust as needed.

6. Instruct the subject to read the provided instructions on how to record a single-lead ECG. The written instructions are:

   a) "It takes 30 seconds to record a measurement. It's important to keep your arms still. Try resting them on a table or your leg. To begin recording rest your finger on the knob."

   b) Practice data will be recorded.

7. After the first practice run, site study staff will guide subject to appropriate study posture and grip (if not achieved independently during the first test run).

8. Allow subject up to three additional practice runs if more practice runs are needed to ensure study posture and grip instruction understanding (fewer than 3 additional practice runs are acceptable if study posture and grip are correct and subject is comfortable with the positioning),

9. Record the number of practice runs completed by the subject. First practice run data and number of practice runs completed by the subject will be used to determine ease of use.

### 5.2.1.2. Data Collection

10. Instruct subject to remain seated for a 5-minute resting period prior to collecting three 12-lead ECGs and set the reference system to 40 Hz filter. Use standard placement of all 12-lead electrodes (with limb lead for Lead 1).

11. Collect 3 separate complete 12-lead ECGs (review to ensure there is no artifact). Each recording will be approximately 30 seconds in duration with a 1-minute rest period between each recording (i.e., 1 minute between the end of the previous recording and the start of the next recording). Simultaneously, instruct the subject to record 3 separate complete single-lead ECGs using the DCD. A total of three complete single-lead ECGs will be collected for each subject. Each recording will correspond to the time of collection of each 12-lead ECG recording.

    c) Monitor the 12-lead waveform to ensure a good quality recording is obtained.

    d) Monitor the waveform from the Lead 1 ECG from the DCD, between ECG recordings, provide feedback to the subject on how to improve the reading.

12. After data collection, instruct study subjects to rate the ease of use of the DCD on a scale of 1-5 (1 being Unable to Use, 2 being Below Average Ease of Use, 3 being Average Ease of Use, 4 being Above Average Ease of Use, 5 being Easiest to Use). Record the rating in the eCRF. Remove DCD from subject.

13. Instruct study subjects to apply and simulate a recording with each of the other devices ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ to rate the comfort and ease of use of each of these devices on a scale of 1-5 (Scale is listed above under #10). Record the ratings.

### 5.2.1.3. Data Processing

14. The Sponsor will receive data files from:

    a) The reference device 12-lead ECG files

    b) Raw data DCD files

15. The Sponsor will check data for Protocol and MOP adherence.

16. For Part A (described below), the Sponsor will sync Lead 1 of the 12-lead (reference strip) to the corresponding SUT's strip to ensure that the same beats from each subject are presented.

17. The Sponsor will provide a portable document format (PDF) of the full 30-second strip of both the reference strips and the SUT's strips on the standard clinical ECG scale to Cardiac Core Lab (for both Part A, Part B-1, and Part B-2).

18. Cardiac Core Lab will print the strips for analysis and distribute to appropriate experts for review.

**5.2.1.4.     Data Review by Cardiac Core Lab** (refer to Operations Plan/ Imaging Charter)

19. **Part A** (To address Objective 2a): Analysis of paired sets of strips.

    a)  The Sponsor will prepare one paired set of strips from approximately 140 randomly selected subjects (70 AF, 70 SR) (approximate strips = 280 strips)

        i.   One set includes a Lead 1 strip from the 12-lead and a paired strip from the SUT.

        ii.  The first reading from data collection will be used for all subjects.

    b)  Cardiac Core Lab review:

        i.   Three blinded, independent cardiac technicians will review each paired set of strips. The strips will be rendered semi-transparent through the use of back lighting and overlaid to visually assess for morphological similarity.

        ii.  One reviewer will identify the first six consecutive distinct readable PQRST complexes without artifact that match between the strips 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 SUT 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 strip 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.

        iii. 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.

        iv.  Measure R amplitude from the isoelectric baseline to the nearest millimeter for the first two QRS complexes in both the reference strip and SUT strip. The reviewers will be blinded to the identity of the reference strip and SUT strip. Record these lengths.

20. **Part B-1** (To address Objective 1): Analysis of reference strips.

    a)  The first reading from 12-lead ECG data collection will be used for all subjects (total strips = ~560). In the event that the planned sample size for analysis is not obtained due to a higher than expected amount of data loss, the 2nd and 3rd reading from data collection may be used as described in the statistical analysis plan (SAP).

    b) Three U.S. board-certified cardiologists out of a pool of nine cardiologists will review each complete 12-lead ECG (reference strip) and provide a diagnosis of the rhythm. (i.e. each reference strip will be reviewed independently 3x)

    c) The diagnosis of the rhythm will fall into one of four categories:

        i.    Sinus rhythm (SR)

        ii.    AF

        iii.    Other specific diagnoses should be called out (examples include normal sinus with premature ventricular contraction [PVC] (if ≥4 beats in the strip), normal sinus with PACS, 2nd degree block, AF with a rate >150 bpm, supraventricular tachycardia [SVT], etc.)

        iv.    Unreadable = a diagnosis cannot be made as the strip is not adequate for reading.

21. **Part B-2:** Analysis of SUT's strips.

    a) The first reading from the SUT's Lead I ECG will be used for all subjects (total strips = ~560).

    b) Two cardiologists out of a pool of five blinded, independent cardiologists will review each of the SUT's strips (single-lead ECG strip generated by the Sponsor's system) and provide a diagnosis. Diagnoses are listed above (Item #20**Error! Reference source not found.** (total strips = ~560)

22. **Part C:** Algorithm classification

    a) The Sponsor will generate a rhythm classification (through use of the algorithm) for the strips that match those strips analyzed in Part B-1 from the SUT for all subjects. (hereon referred to as algorithm classification) (total strips = ~560)

    b) The rhythm classification generated by the algorithm will fall into one of four categories:

        i.    Sinus rhythm (SR)

        ii.    AF

        iii.    Unclassifiable = Other specific diagnoses which are not AF or SR (examples include normal sinus with premature ventricular contraction [PVC] (if ≥4 beats in the strip), normal sinus with PACS, 2nd degree block, AF with a rate >150 bpm, supraventricular tachycardia [SVT], etc.)

        iv.    Unreadable = a classification cannot be made as the strip is not adequate for reading.

    **c)** The Core Cardiology Lab will not review the classifications.

# STATISTICAL ANALYSIS

## 5.3.    Statistical Methodology and Determination of Sample Size

### 5.3.1.    Primary Objective/Endpoint

The primary endpoints of this study are the sensitivity in detecting AF and specificity in detecting SR on readable/ classifiable strips (i.e., resulting in a diagnosis of AF or SR) generated by the single Lead I ECG of the SUT using the 12-lead ECG monitor GE Healthcare CardioSoft ECG device (K031561) as the Reference. The primary hypotheses for sensitivity and specificity are as follows:

$H_{01}$: $\Pi_{Sen} = 0.90$
vs.
$H_{A1}$: $\Pi_{Sen} > 0.90$

$H_{02}$: $\Pi_{Spec} = 0.92$
vs.
$H_{A2}$: $\Pi_{Spec} > 0.92$

### 5.3.2.    Secondary Objectives/Endpoints

Two hypotheses associated with secondary objective 2a to demonstrate that the SUT produces a waveform that provides clinically equivalent information to the gold standard Reference will also be tested.

The first hypothesis is aimed at demonstrating that the proportion of subjects with a pass rating based on the visual assessment of 6 consecutive readable PQRST complexes is at least 80%. The majority result from the pass/fail readings of the three independent cardiac technicians will be used for analysis. The hypothesis for this objective can be stated as follows:

$H_{03}$: $\Pi_1 = 0.80$
vs.
$H_{A3}$: $\Pi_1 > 0.80$

where $\Pi_1$ represents the true population subject success proportion of pass ratings.

The second hypothesis associated with objective 2a is based on the results of the quantitative analysis of the R-wave amplitudes as measured by each of three cardiac technicians on the paired SUT and Reference strips in Part A.  The majority result from the three technicians (i.e., if at least two technicians measure the  difference in amplitudes between the SUT and reference strip to be ≤2mm, then the paired strips for a given subject will be deemed ≤2mm) will be used for testing the hypothesis that the proportion of paired R-Wave amplitude measurements ≤ 2 mm of each other is at least 80%

$H_{04}$: $\Pi_2 = 0.80$
vs.

$H_{A4}$: $\Pi_2 > 0.80$

where $\Pi_2$ represents the true population agreement proportion of paired R-Wave amplitude measurements. For each participant, 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.

### 5.3.3    Sample Size

Under the assumption that the true population sensitivity is 95%, 231 subjects who are diagnosed with AF based on the 12-lead ECG reference strip and where the device algorithm classification produces a result of AF or SR will provide at least 80% power to reject its null hypothesis, $H_{01}$, using a one-sided type I error of 0.025. Moreover, under the assumption that the true population specificity is 96.5%, 226 subjects who are diagnosed with SR based on the 12-lead ECG reference strip and where the device algorithm classification produces a result of AF or SR will provide at least 80% power to reject its null hypothesis, $H_{02}$, using a one-sided type I error of 0.025. To account for obtaining readable waveforms, a minimum of 260 subjects with a known diagnosis of AF and approximately 300 subjects with no known diagnosis of AF will be enrolled.  The sample size for AF subjects may be increased if the unreadable/unclassifiable rate is higher than originally assumed up to a maximum of 400 enrolled AF subjects.

For the secondary objective hypothesis, $H_{03}$, under the assumption that the true population subject success rate is 90%, 88 subjects will provide at least 80% power to reject its null hypothesis using a one-sided type I error of 0.05. To account for obtaining readable waveforms, approximately 140 subjects (70 SR; 70 AF) will be randomly selected.

### 5.3.4    Randomization and Blinding

This study is not randomized. Cardiac technicians will be blinded in Part A and will not know which strip is the Reference vs SUT strip. U.S. board-certified cardiologists in Part B-1 and board-certified cardiologist in Part B-2 will be blinded to the subject's past medical history and algorithm classification.

Approximately 140 subjects (70 SR; 70 AF) will be randomly selected to address objective 2a in Part A using a systematic sampling approach.  A number between 1 and 4 will be randomly selected for the AF cohort and then every 4th consecutively enrolled AF subject will be selected at random within each site. Likewise, a number between 1 and 4 will be randomly selected for the SR cohort and then every 4th consecutively enrolled SR subject will be selected at random within each site.

### 5.3.5    Significance Level

The primary hypothesis tests of sensitivity and specificity will use a one-sided significance level of 0.025. The hypothesis tests, $H_{03}$, and $H_{04}$, associated with the secondary objectives will use a one-sided significance level of 0.05.  Multiple comparison corrections will not be used.

### 5.3.6    Missing Data/Outliers

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 readable or obtainable. The data analyses will be conducted on all readable/classifiable data. Outliers may be removed from the analyses after investigation by the sponsor and biostatistician; any removal of data points from the analyses will be documented in the CSR. No outliers will be removed from the analyses of the primary or secondary endpoints.

### 5.3.7    Subgroup Analyses

In accordance with the FDA Guidance[8] on the reporting of age-, race-, and ethnicity-specific data, the sensitivity and specificity (primary endpoint) will be reported by the following subgroups (data permitting). Some subgroups may be combined depending on data availability.

- Age group (22-30, 31-50, 51-64, and 65+)
- Sex (M/F)
- 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)

### 5.3.8    Interim Analyses

There are no interim analyses planned in this study. There will be a planned interim data transfer after enrollment of 50 subjects for study progress monitoring purposes. None of the study hypotheses will be tested at this interim data transfer.

### 5.3.9    ANALYSIS SETS

Based on the results of the 12-lead ECG at screening, a minimum of 260 subjects are targeted to be enrolled into an AF cohort and approximately 300 subjects are targeted to be enrolled into a SR cohort to address objective 1. Approximately 140 of these subjects (70 SR; 70 AF) will be randomly selected to address objective 2a in Part A. The following analysis sets are defined for this study.

All Enrolled Analysis Set: All subjects who sign informed consent and are enrolled into the study. This analysis set will be used to summarize subject and ECG measurement accountability, demographic and baseline characteristics, safety data, and the ease of use data.

Classifiable Analysis Set: All subjects who have readable/classifiable paired SUT and Reference strip from Parts C and B-1, respectively. This analysis set will be used for analyzing the primary endpoints of sensitivity and specificity.

Waveform Assessment Analysis Set: Randomly selected subjects in Part A with paired SUT and Reference strips. If 6 consecutive paired beats for analysis cannot be found in these strips, they will be excluded from further analysis. This analysis set will be used for assessing the quality of the clinical waveform associated with secondary objective 2a.

# 6.     SAFETY PARAMETERS AND ASSESSMENT

## 6.1.     Adverse Events

The definition of adverse events are as follows,

Adverse event - An adverse event is any untoward medical occurrence in a study subject which does not necessarily have to have a causal relationship with the study procedures.

An AE can therefore be any clinically significant sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the study procedures, whether or not considered related to the study procedures.

## 6.2.     Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may jeopardize the subject or may require intervention [e.g. medical, surgical] to prevent one of the other serious outcomes listed in the definition above.

Unanticipated Adverse Event - Any serious adverse effect on health or safety or any Life-threatening problem or death caused by, or associated with the study treatment, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the patient.

### 6.2.1.     AE/SAE Collection

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. Signs and symptoms of each AE should be described in detail: onset time and date, offset time and date, description of event, severity, relationship to study procedures, action taken and outcome. Adverse events will be collected as spontaneously reported by the subjects.

### 6.2.2.     SAE Reporting

SAEs occurring on this study will be reported by the Investigator to the Sponsor and the IRB within 24 hours of becoming aware of the event. The Investigator will be requested to complete a separate SAE reporting form in addition to the information in the source documentation.

## 6.3. Intensity of Adverse Events

The intensity of an AE will be categorized as follows:

- Mild: Events that are easily tolerated with no disruption of normal daily activity

- Moderate: Events that cause sufficient discomfort to interfere with daily activity

- Severe: Events that incapacitate and prevent usual activity

## 6.4. Causal Relationship Assessment

Causal relationship assessment to study procedures is required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into considerations along with good clinical and scientific judgment when determining the relationship of study procedures to an AE:

- Definitely Related: A clinical event, including laboratory test abnormality, occurring in a plausible temporal relationship to the study procedures, and which cannot be explained by concurrent disease or other drugs or chemicals.

- Possibly Related: A clinical event, including laboratory test abnormality, with a reasonable temporal relationship to the study procedures, but which could also be explained by concurrent disease or other drugs or chemicals.

- Unlikely Related: A clinical event, including laboratory test abnormality, with little or no temporal relationship to the study procedures, and which could be explained by concurrent disease or other drugs or chemicals.

- Not Related: A clinical event, including laboratory test abnormality, that has no temporal relationship to the study procedures.

**Action Taken**

Action taken will be defined as:

- None

- Study procedures interrupted

- Study procedures stopped

## 6.5. Outcome

Outcome will be defined as:

- Resolved

- Ongoing or stabilized and followed by private MD

- Lost to follow up

## 6.6.        Safety Plan

The clinical staff is responsible for the ongoing safety and well-being of the subjects while they are in the clinical unit. Management of all medical complications arising during the course of the research study will be managed by the investigator as deemed appropriate. 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 the 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.      REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

## 7.1.      Institutional Review Board

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, informed consent, and all other forms of subject- and reviewer-related materials be reviewed by an IRB. IRB approval of the protocol, informed consent and subject information and/or advertising will be obtained prior to study initiation. Any amendments to the protocol will require IRB approval prior to the implementation of any changes to the study design.

## 7.2.      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 Conference on 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 (and/or relatives, guardians, or legal representatives, if necessary) 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.

## 7.3.      Ethical Conduct of Study

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).

## 7.4.      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 subject-anonymized 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.

## 7.5.        Data 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 lead 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 and SUT will be controlled and the SUT 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 data collection devices and SUT.

## 7.6.        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.

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 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, the 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. 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.

## 7.7.        Data Quality Assurance and Quality Control

The Sponsor or designee will provide and maintain a charter that describes the independent review and training process for reviewers. This will include, but is not limited to:

- Project Objective and Overview
- Acquisition Standards
- Data Transfer Process
- Monitoring Plans

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.

## 7.8.        Use of Information

All information concerning the SUT 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 SUT. 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.

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.

## 7.9.        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 SUT 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.

## 7.10.    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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